ANNUAL REPORTS

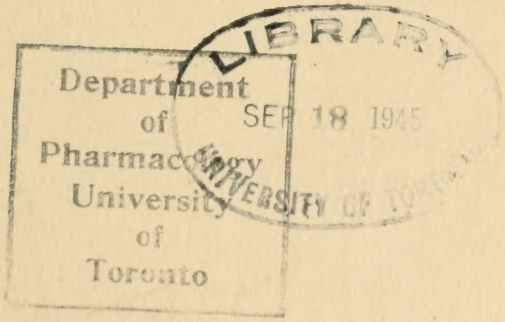
OF THE

CHEMICAL LABORATORY

OF THE

AMERICAN MEDICAL ASSOCIATION

VOLUME 14. JAN.-DEC. 1921



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JANUARY-DECEMBER, 1921

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AMERICAN MEDICAL ASSOCIATION

FIVE HUNDRED AND THIRTY-FIVE NORTH DEARBORN STREET

CHICAGO

PREFACE

The Chemical Laboratory of the American Medical Association was established in 1906 to assist the Council on Pharmacy and Chemistry of the American Medical Association in the investigation of proprietary and unofficial non-proprietary medicinal preparations offered to the medical profession.

In accordance with the object of its foundation, the A. M. A. Chemical Laboratory concerns itself primarily with the examination of those proprietary and unofficial medicinal preparations which the Council has under consideration. The Laboratory determines if the claims made for the composition of these preparations are truthful, and, when a product is admitted to the Council's publication "New and Nonofficial Remedies," looks after the establishment of standards whereby the identity and purity of such a product may be determined.

In addition to the investigations made for the Council on Pharmacy and Chemistry, the Laboratory aids The Journal of the American Medical Association in supplying the medical profession and the public with information about the character and composition of drugs. This includes the analyses of proprietary medicinal preparations which are offered to the medical profession and which are not deemed worthy of investigation by the Council on Pharmacy and Chemistry, and the analyses of nostrums ("patent medicines") exploited to the public. Through the columns of The Journal and through direct correspondence the Laboratory responds to requests of physicians for information regarding proprietary preparations advertised to physicians and quack nostrums sold to the public, which have come to their notice. A knowledge of the composition of nostrums, whether offered to the medical profession or to the lay public, is generally a sufficient demonstration that many of the therapeutic claims made for such preparations are unwarranted. For this reason the Laboratory strives earnestly to answer all such inquiries, either by reference to avail-

able information or by actual analysis, when it is believed that the results of such investigation will prove of general interest to the medical profession or to the public.

This volume of the Reports of the A. M. A. Chemical Laboratory contains those portions of the Laboratory's activities during 1921 which were believed to be of interest to workers concerned with the examination and standardization of medicines, and includes: (1) reprints of contributions from the Chemical Laboratory of the American Medical Association, (2) reports abstracted from The Journal of the American Medical Association and (3) reports not previously published. Continuing the practice adopted at the foundation of the Laboratory, each report in this volume contains a detailed statement of the analytical methods employed and the results obtained, whenever it was believed that such statement would prove helpful to others engaged in the examination of medicines.

The quantitative separation of strychnin from quinin has attracted the attention of analysts for many years. The paper reprinted on page 7 demonstrates the inaccuracy of one of the published methods. The investigation of the question whether Kalnite contains the double salt, potassium aluminum nitrate, is an illustration of the aid which the Laboratory gives to the Council on Pharmacy and Chemistry in attempting to prove or disprove unusual chemical claims. Tentative standards for the identity and purity of a number of medicinals have been prepared. Among these are benzyl succinate, anhydrous dextrose, potassium mercuric iodid and theobromin sodium acetate. Considerable hitherto unpublished information is given concerning the chemical properties of methyl atropin bromid (*mydriasine*) and benzyl succinate. The items on "Modified Salicylic Acid," Iodinol and Samarin should prove interesting to those concerned with the enforcement of drug laws. Preparations containing phenobarbital (luminal) are being sold as epilepsy remedies. Several of these have been examined. The chemistry and pharmacy of effervescent salts is discussed in connection with the analysis of Sal Hepatica.

CONTENTS

PART I

REPRINTS OF CONTRIBUTIONS FROM THE CHEMICAL LABORATORY OF THE AMERICAN MEDICAL ASSOCIATION

NOTES ON THE BLISS METHOD FOR THE SEPARATION OF STRYCHNIN FROM QUININ

(Reprinted from the Journal of the American Pharmaceutical Association, April, 1921, p. 267)

L. E. Warren, Ph.C., B.S., and A. H. Clark, Ph.C., B.S.

A case having arisen in the experience of one of the writers (A. H. C.) in which an accurate separation of strychnin from quinin became desirable, the applicability of the method published by A. R. Bliss[1] was considered. As a preliminary, a mixture of quinin and strychnin in unknown proportions was tested by the method. The results obtained by the qualitative tests on the mixture were unsatisfactory. The fraction supposed to be quinin contained strychnin and the remaining fraction (supposed to be strychnin) contained quinin. Since the findings for the unknown mixture were so unsatisfactory, it seemed worth while to have the method checked on a known mixture of the two alkaloids.

In theory, the Bliss method is based primarily on the ready solubility of quinin in ether (1 in 1.5) and the scant solubility of strychnin in this solvent (1 in 5,500). Secondarily it depends on the solubility of strychnin in water (1 in 6,420). Although the solubility of strychnin is greater in ether than in water, the method requires a sufficient volume of water to dissolve all of the strychnin while permitting the use of but small volumes of ether. As recommended by Bliss, the total alkaloids are obtained in the usual way, weighed and dissolved in dilute sulphuric acid. An excess of water (more than 6,500 times the weight of strychnin supposed to be present) is added, the solution made alkaline with ammonia water, and the mixture shaken seven times with small portions of ether, using 35 c.c., 20 c.c., 10, 10, 10 and 5 c.c.,

1. Bliss, A. R.: A Method for Estimating Quinin and Strychnin When Occurring in Common Solution, J. Am. Pharm. Assn. **8**: 804, 1919.

respectively. The combined ether solutions are washed with water, evaporated, the residue dried with the usual precautions and weighed as quinin. The ammoniacal liquid in the separator is then shaken with successive portions of chloroform, the solvent evaporated, the residue dried and weighed as strychnin. All of the determinations reported by Bliss were made on a mixture containing about thirty-two times as much quinin as strychnin, *i. e.*, determinations were not reported on mixtures containing other proportions of the two alkaloids.

A solution was prepared by dissolving 10.0286 gm. of quinin and 0.9851 gm. of strychnin in hydrochloric acid and diluting the solution to 500 c.c. with distilled water. Each c.c. of this solution contained 0.020057 gm. of quinin (alkaloid) and 0.00197 gm. of strychnin (alkaloid), the latter being present in approximately one-tenth of the concentration of the former. Two samples of 10 c.c. each from this solution were assayed strictly according to the method as published by Bliss. Sample A gave 0.2216 gm. of alkaloid in the fraction supposed to be quinin and 0.0023 gm. of alkaloid in the strychnin fraction. These values are equivalent, respectively, to 110.5 per cent. of theory for quinin and 11.7 per cent. of theory for strychnin. Sample B gave 0.2151 gm. for the quinin residue and 0.0049 gm. for the strychnin fraction, equivalent, respectively, to 107.3 per cent. of theory for quinin and 24.9 per cent. of theory for strychnin.

The residue from Sample A as obtained in the preceding paragraph, supposed to be quinin, was dissolved in a slight excess of sulphuric acid, a 5 per cent. solution of potassium ferrocyanid[2] added, the mixture agitated and allowed to stand over night. A noticeable precipitate formed. This was collected on a filter, the filter suspended in water, a slight excess of ammonia water added and the mixture shaken with chloroform until extraction was complete. The chloroform fractions were united, washed with a little water, the solvent evaporated, the residue dried and weighed. The residue weighed 0.0142 gm. equivalent to 72.1 per cent. of the theoretical amount of strychnin originally taken in Sample A. This residue gave the "fading purple" test for strychnin, thus showing that the method of separation of the quinin from the strychnin as carried out by the Bliss method was not quantitative and that the ferro-cyanide method was more nearly exact.

2. Simmonds, C.: Analyst **39**: 81, 1914.

Another determination was carried out on 50 c.c. of the above-described alkaloidal solution (equivalent to 1.00286 gm. of quinin and 0.09851 gm. of strychnin). The results were 1.0708 gm. for the quinin fraction, equivalent to 106.8 per cent. of theory, and 0.0274 gm. for the strychnin fraction, equivalent to 27.8 per cent. of theory.

In order that the determinations might be made upon mixtures containing other proportions of quinin and strychnin than in those previously used, another solution was prepared by dissolving 3.0527 gm. of quinin and 0.1964 gm. of strychnin in dilute sulphuric acid and diluting the solution to 1,000 c.c. Each c.c. of this solution contained 0.0030527 gm. of quinin and 0.0001964 gm. of strychnin. The concentration of quinin is approximately fifteen times that of the strychnin. Assays by the Bliss method were made upon 100 c.c. portions of this solution. Sample A gave 0.3191 gm. for the quinin fraction, or 104.5 per cent. of theory and 0.0054 gm. for the strychnin portion, or 27.5 per cent. of the amount taken. Sample B gave 0.3083 gm. for the quinin fraction, or 101.0 per cent. of the quantity taken, and 0.0158 gm. for the strychnin portion, or 80.4 per cent. of theory.

A solid mixture containing 81.52 per cent. of quinin and 18.48 per cent. of strychnin was prepared. This mixture was assayed by the Bliss method by each author independently. In one assay (A. H. C.) 0.0885 gm. of the mixture (equivalent to 0.07215 gm. of quinin and 0.01635 gm. of strychnin) gave 0.0838 gm. of extract supposed to be quinin and 0.0038 gm. of extract supposed to be strychnin. The values are, respectively, 116.1 per cent. and 23.2 per cent. of theory. In another experiment 0.300 gm. of the mixture was shaken once with 50 c.c of ether. On evaporation the solvent gave 0.2560 gm. of residue, equivalent to 85.3 per cent. of the total alkaloid taken or 104.7 per cent. of the quantity of quinin taken. This fraction contained an abundance of strychnin. No attempt was made to recover the strychnin by completing the second stage of the assay.

In another assay of the above-described solid mixture by the Bliss method (L. E. W.) 0.6032 gm. of material, equivalent, respectively, to 0.49173 gm. of quinin and 0.11147 gm. of strychnin, gave, respectively, 0.5688 gm. supposed to be quinin and 0.0318 gm. supposed to be strychnin. These values are respectively, 115.7 per cent. and 28.5 per cent. of the quantities taken. The quinin fraction contained an abundance of strychnin, as shown by the ferrocyanid and shakeout test

already described. The strychnin fraction appeared to be practically free from quinin as shown by the very scant fluorescence of its solution in very dilute sulphuric acid.

Other assays by the Bliss method were made, using solutions as follows:

A solution containing 0.50248 gm. of quinin and 0.01964 gm. of strychnin was prepared. The quinin fraction weighed 0.5136 gm. or 102.2 per cent. of theory. The strychnin fraction weighed 0.0067 gm., or 34.1 per cent. of the quantity taken. Another solution containing 0.6139 gm. of quinin and 0.01964 gm. of strychnin was prepared. In this mixture the alkaloids are present in approximately the same proportions as in the

SEPARATION OF STRYCHNIN FROM QUININ—BLISS METHOD

	Weight Taken	Weight Recovered	Percentage Recovered	Remarks
Quinin.....	0.20057	0.2216	110.5	Contained strychnin
Strychnin.....	0.0197	0.0023	11.7	
Quinin.....	0.20057	0.2151	107.3	
Strychnin.....	0.0197	0.0049	24.9	
Quinin.....	1.00286	1.0708	106.8	Contained strychnin
Strychnin.....	0.0985	0.0274	27.8	
Quinin.....	0.30527	0.3191	104.53	
Strychnin.....	0.01964	0.0054	27.5	
Quinin.....	0.30527	0.3083	101.0	
Strychnin.....	0.01964	0.0153	80.5	
Quinin.....	0.07215	0.0838	116.1	
Strychnin.....	0.01635	0.0038	23.2	Contained quinin
Quinin.....	0.24456	0.2560	104.7	Contained strychnin
Strychnin.....	0.05544	Not recovered		
Quinin.....	0.49173	0.5688	115.7	Contained strychnin
Strychnin.....	0.11147	0.0318	28.5	
Quinin.....	0.50248	0.5136	102.2	Contained strychnin
Strychnin.....	0.01964	0.0067	34.1	Free from quinin
Quinin.....	0.6139	0.6222	101.3	Contained strychnin
Strychnin.....	0.01964	0.0123	62.6	

solution assayed by Bliss. In the assay this solution gave 0.6222 gm. for the quinin fraction and 0.0123 gm. for the strychnin value. These findings are equivalent, respectively, to 101.3 per cent and 62.6 per cent of the quantities taken. The quinin fraction contained strychnin, as shown by the ferrocyanid test. For comparison the several findings are tabulated herewith.

It is believed that the portions of quinin and strychnin used in these experiments have been varied sufficiently to be representative of conditions likely to be met with in the analysis of medicines. From the results obtained it appears evident that the method is unsuitable as a quanitative procedure for the separation of the two alkaloids. It does not compare

favorably with the ferrocyanid method of separation. In general, the smaller the proportion of strychnin in the mixture the more nearly is the completeness of the separation.

It is known that the presence of large amounts of quinin in strychnin interferes with the oxidation color reactions by which the latter alkaloid is identified. By removing most of the quinin from mixtures of the two alkaloids, as is possible by a careful working of this process, the strychnin may be obtained in a state sufficiently pure for identification. The Bliss method, therefore, may be found useful in the qualitative analysis of medicines, although it appears to have no advantage over the well-known ferrocyanid method.

PART II

REPORTS ABSTRACTED FROM THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, AND FROM THE ANNUAL REPORTS OF THE COUNCIL ON PHARMACY AND CHEMISTRY

TONA-VIN

(Abstracted, with additions, from the Journal A. M. A., Jan. 15, 1921, p. 193)

A sample specimen of Tona-Vin was obtained from the Associated Advertising Clubs of the World. It was one of the "free trial" ounce bottles which were being distributed to the public. The main label described Tona-Vin as "The Iron Tonic" and:

"A System Tonic and Strengthener."

"A Palatable and Energizing Treatment containing soluble Iron and Quinine, Fluid Extract of Senna Leaves, Wild Cherry and Aromatics."

The label also admitted the presence of 18 per cent. of alcohol. The directions (for adults) called for "One to two tablespoonfuls before meals" and added that the "dose may be *increased* or *lessened* [italics ours] according to its action in the bowels." The lower part of the label bore this statement:

"Manufactured For Thomas Chemical Co. Under U. S. Bureau of Internal Revenue Department Permit No. Pa. H-11057."

On the reverse side of this free trial bottle was a small label (reproduced with this article) reading:

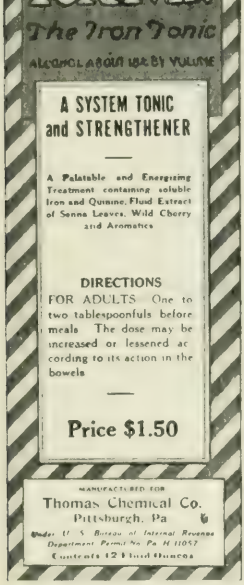
"We hereby certify that this product was made under our supervision and complies with the provisions of the National Prohibition Act and the Regulations of the Prohibition Commissioners. AMERICAN STANDARDIZING BUREAUS, Washington, D. C.

"CAUTION—This preparation has been made with non-beverage alcohol and the sale or use thereof for beverage purposes will render the vendor or user liable to severe penalties."

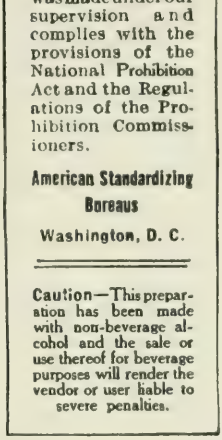
The liquid in the "free trial bottle" tasted like wine with a dash of wild cherry and just a suspicion of bitters. As evidently it had all the necessary elements of a good "repeater" it was decided to examine the product in greater detail.

A market specimen of Tona-Vin was examined in the Association's Laboratory and the following report published in THE JOURNAL:

"Tona-Vin is a dark-brownish liquid, having an odor like wild cherry and wine, and a slightly bitter, somewhat sour taste. The label states that the preparation contains 'soluble



Reproduction (greatly reduced) of the main label of "Tona-Vin."



Reproduction (full size) of the "certificate" that appears on the "free trial bottles" of "Tona-Vin." The "American Standardizing Bureaus" has nothing to do with the government. It is a private concern, one of whose functions seems to be the devising of "formulas." It also sees to it that in the marketing of such products the letter of the law is observed.

iron and quinin, fluid extract of senna leaves, wild cherry and aromatics.' The presence of 18 per cent. of alcohol is admitted. The package contains slightly less than 11 fluid ounces, although the label declares the contents to be 12 fluid ounces. As a matter of fact the Tona-Vin bottles will not hold 12 fluid ounces.

"Tona-Vin is acid to litumus. On evaporation, the preparation gave 11.42 gm. of residue per 100 c.c. Phenolphthalein, bromids, iodids, and the purgative salts, such as magnesium sulphate and sodium phosphate were absent. Alkaloids, iron and extractives from an emodin-bearing drug were found, the latter in noticeable amounts.

"The total alkaloids amounted to 0.0222 gm. per 100 c.c., or about 1/10 gr., per fluidounce. The alkaloids appeared to consist chiefly of quinin. Although the circular which accompanies the trade package of Tona-Vin states that nux vomica is one of the ingredients of the preparation, no mention of this drug is made on the label and tests for strychnin and brucin (normal constituents of nux vomica) were negative. The U. S. P. 'tonic dose' of quinin is 1½ grains; hence a dose of Tona-Vin (1 fluidounce) contains about 1/15 of a dose of quinin, and to obtain a tonic dose of this drug, the individual would be required to drink the contents of about 1.4 bottle of the preparation. This is equivalent in alcoholic content to about 7.4 fluidounces of whisky. The absence in Tona-Vin of quinin in therapeutically effective quantities is demonstrated by the fact that the preparation is only very slightly bitter.

"Iron was determined, the amount found corresponding to the equivalent of 0.02 gm. of metallic iron per 100 c.c., or about 9/100 grain per fluidounce. The U. S. P. dose of reduced iron is 1 grain; hence a dose of Tona-Vin contains 1/11 of a dose of iron and, to obtain an average does of this drug, the individual would be obliged to drink the contents of an entire bottle of Tona-Vin. One fluidounce (one dose) of Tona-Vin was dealcoholized by evaporation and the residue swallowed by a healthy man. No effect except a doubtfully laxative action resulted. This test, in conjunction with the chemical examination, indicates that Tona-Vin is not sufficiently medicated to prevent its use in moderate amounts as a beverage."

Concerning the manufacturer of Tona-Vin, The Thomas Chemical Company, and the "American Standardizing Bureaus" under whose supervision the preparation is made, THE JOURNAL commented as follows:

"The gist of the chemists' report lies in the closing sentence. There is, of course, no legitimate reason for administering such drugs as iron, quinin and senna in ridiculously small doses in a menstruum containing 18 per cent. of alcohol. Any of these three drugs can be administered in tablet form.

Their sale in the form of Tona-Vin simply gives one more loophole to evade the regulations of the national prohibition law.

"THE THOMAS CHEMICAL COMPANY

"There were still three points regarding the exploitation of Tona-Vin that needed clearing up. First: Who and what is the Thomas Chemical Co., under whose name the stuff is sold? We are advised that the Tona-Vin advertisements have been placed by the Charles H. Fuller Co., a Chicago advertising agency, and that the newspapers that carried the advertisements were instructed to send copies of the issues containing the advertisements to W. & H. Walker, Inc., Pittsburgh, Pa. The Walker concern is listed as a manufacturer of soap and toilet articles. The Thomas Chemical Co. on its letterheads describes its business as 'Flavoring Extracts, U. S. P. Preparations and Proprietary Medicines.' Just why a manufacturer of soap and toilet articles should create a subsidiary company to exploit an alcoholic 'patent medicine' we will leave for it to explain.

"THE AMERICAN STANDARDIZING BUREAUS

"Another point of interest was the 'American Standardizing Bureaus' of Washington, D. C., whose 'certificate,' that Tona-Vin was made under their supervision, appears on the 'free trial' bottles. The American Standardizing Bureaus, in spite of its name and the fact that it is at Washington, has nothing to do with the government; it is purely a private organization. It occupies three rooms on the fifth floor of an office building. We are advised that it is a partnership affair and to its chief owner, it is alleged, belongs the distinguished honor of outlining the formula for this 'Wonderful Body Strengthener, Stomach Settler, Appetizer and Liver Regulator.' It seems that the American Standardizing Bureaus have one of their employees at the Walker headquarters supervising the preparation of Tona-Vin and that it is the business of the 'bureaus' to see that care is taken that all legal and regulatory restrictions are observed.

"GETTING AN OFFICIAL O.K.

"Finally: the full size of Tona-Vin bears this statement at the head of the secondary label on the bottle:

'Formula Approved by the United States Bureau of Internal Revenue, April 29, 1920, Serial No. of Permit Pa. H-11057.'

"In view of this a letter was written to the Chief of the Bureau of Internal Revenue at Washington, apprising him of

the results of the investigation of the A. M. A. Chemical Laboratory and of the claims made for Tona-Vin. Then this question was asked:

> 'If it is not against the policy or rules of the Bureau, will you let us know, first, whether the permit was issued to the Thomas Chemical Co. as such, or to some other concern that stood sponsor for the Thomas Chemical Co., and, second, whether in issuing these permits any investigation is made of the bona fides of the company or concern to whom such permits are issued?'

"In reply, a courteous letter was received from Assistant Prohibition Commissioner, D. S. Bliss, stating that 'Tona-Vin' was manufactured under permit issued to W. & H. Walker, Pittsburgh, Pa. The reply continued:

> 'In answer to your second question as to whether or not investigation is made of the bona fide character of the company to whom such permits are issued, you are informed that each state Prohibition Director is supposed to make a thorough investigation before approving an application for a permit under the Volstead Act. If you wish to file a complaint against the manufacture and sale of this preparation, as being in violation of the Volstead Act, the office would appreciate the same.'

"Here, then, we have the whole business. A concern whose business is the marketing of soaps and toilet articles goes into the manufacture of a nostrum whose chief and most potent ingredient is alcohol—this, too, at a time when the use of alcohol as a beverage has been prohibited by the Constitution of the United States and by special legislation of Congress. This nostrum seems to have been devised presumably at the request of the company that manufacturers it and makes money out of it and doubtless for a handsome consideration, by men of supposed professional standing. The 'formula' thus evolved is given an official O. K. by the state prohibition director and the stuff is put on the market. Certain newspapers sell whole pages to the nostrum manufacturer in order to acquaint the public with this new 'tonic' which 'Puts Dash and Go into Tired, Weary, Sick and Run-down Men and Women.' Thousands of bottles of the stuff are given away in order to acquaint the public with its 'virtues.'

"A beautiful business; and all perfectly legal!"

Details of Analysis

Residue on Drying.—Ten c.c. of the preparation were evaporated to dryness on a water bath, the residue dried at

100 C. and weighed. From 10 c.c. a residue of 1.1421 gm. was obtained, equivalent to 11.42 gm. per 100 c.c.

Total Alkaloids.—A measured quantity (250 c.c.) was diluted with an equal volume of water and the solution evaporated to about 200 c.c. The residue was made alkaline with ammonia water and shaken with successive portions of chloroform until extraction was complete. The several portions of chloroform were united and the bulked solvent shaken with small portions of very dilute hydrochloric acid until all of the alkaloids were removed from the chloroform. The acid fractions were united, evaporated to small volume, filtered, the filtrate made alkaline with ammonia water and shaken with several portions of a mixture of chloroform and ether, until extraction was complete. The solvent was evaporated, the residue dried at 100 C. and weighed. From 250 c.c. of the preparation 0.0556 gm. of alkaloid was obtained, equivalent to 0.0222 gm. per 100 c.c. This residue responded to qualitative tests for quinin. The alkaloidal residue was dissolved in very dilute hydrochloric acid, the solution diluted to 40 c.c. with water, made alkaline with ammonia water and shaken with seven small portions of ether. The aqueous solution was then shaken with chloroform, the solvent evaporated and the residue, which was very small, was treated with a few drops of sulphuric acid and a fragment of potassium dichromate. No purple color was given. This was taken to indicate the absence of strychnin. The recommended dose of Tona-Vin is "one to two tablespoonfuls." The maximum recommended dose of Tona-Vin (two tablespoonfuls or one fluidounce), contains but $\frac{1}{10}$ grain of total alkaloids. The U. S. P. tonic dose of quinin is $1\frac{1}{2}$ grains or at least 15 times greater than can possibly be present in a dose of Tona-Vin, even granting that all of the alkaloids present are quinin.

Iron.—A sample of 250 c.c. was evaporated to dryness, the residue burned, the ash digested with a mixture of nitric and hydrochloric acids, the solution evaporated almost to dryness, the residue diluted with water and filtered. The filtrate was evaporated repeatedly with an excess of hydrochloric acid to remove traces of nitric acid, the final solutions treated with potassium iodid and the liberated iodin titrated with tenth-normal sodium thiosulphate. The iodine liberated from 250 c.c. of the original material required, 8.4 c.c. of tenth-normal sodium thiosulphate, equivalent to 0.01962 gm. of iron per 100 c.c., or about $\frac{9}{100}$ grain per fluidounce.

Emodin-Bearing Drugs.—A quantity of the material (about 10 c.c.) was evaporated to remove alcohol, the residue acidified

with hydrochloric acid and the solution shaken with ether. The ethereal solution was washed first with water and afterward with very dilute ammonia water. A red color in the alkaline layer indicated the presence of emodin-bearing drugs.

Contents of the Container.—One of the bottles which had contained Tona-Vin was filled with water to the neck and the contents measured. In one test 304 c.c. were required and in a duplicate 308 c.c. This is equivalent to about 10.41 fluidounces. The content declared on the package is 12 fluidounces.

SALICON

(Abstracted, with additions, from The Journal A. M. A., Feb. 5, 1921, p. 397)

"Salicon" is marketed by the K. A. Hughes Company, Boston, as "an improved aspirin." In a circular sent out to the public a little over a year ago the following claims were made for it:

"We rendered aspirin absolutely harmless and yet retained all its virtues as a medicine."

"It positively will not depress the heart nor upset the stomach no matter how large amounts of it are taken."

". . . the Massachusetts state medical authorities . . . adopted its use at all the state camps for fighting the Spanish influenza . . ."

The first two statements quoted above are obviously false. The third statement might have been true although it seemed unlikely. A letter was, therefore, written by THE JOURNAL to the Department of Public Health of the Commonwealth of Massachusetts and the claim of the K. A. Hughes Company relative to the adoption of Salicon in all the state camps by the "state medical authorities" was brought to their attention. The reply of the department on this point was emphatic:

"The State Department of Health of Massachusetts did not endorse the use of Salicon for any purpose."

Some Salicon was purchased on the open market. In due time the following report was made:

One original bottle of "Salicon" (K. A. Hughes Company, Boston) was submitted by the Propaganda department of THE JOURNAL to the Association's Chemical Laboratory for examination. The bottle contained 100 white tablets having an average weight of 0.407 gm. (6.3 grains) each. The amount of ash was 20.9 per cent. Qualitative tests indicated the presence of magnesium, carbonate, starch, acetylsalicylic acid and a trace of calcium; a very small amount of a petrolatum-like substance was present. Alkaloids and drugs used for a

laxative effect were not found. The amount of acetylsalicylic acid extracted by chloroform was 50.7 per cent. The amount of magnesium present as magnesium oxid was 14.3 per cent. The amount of magnesium oxid derived from magnesium carbonate U. S. P. is variable but calculating on the lowest limit, 14.3 per cent. of magnesium oxid is equivalent to at least 35.5 per cent. of magnesium carbonate. This figure agreed closely with that obtained from the U. S. P. method of assay. The acetylsalicylic acid was not combined with the magnesium. From the above, it may be stated that each tablet consisted essentially of a mixture of 3.2 grains of acetylsalicylic acid (aspirin), 2.2 grains of magnesium carbonate and some starch. Although labeled 5 grains, each tablet did not contain 5 grains of the most active ingredient, acetylsalicylic acid.

As THE JOURNAL said:

"The same old story. An ordinary mixture of well-known drugs put on the market as a new discovery and foisted on the public under false and misleading claims."

"MODIFIED SALICYLIC ACID" AND "SAMARIN"

(Reprinted, with additions, from The Journal A. M. A., March 26, 1921, p. 883)

The attention of the Laboratory was called to "Modified Salicylic Acid" and "Samarin" put out by the Frank S. Betz Co. of Hammond, Ind. Both are described in the Betz pharmaceutical catalogue but no information is given concerning their composition. In general the Betz pharmaceuticals are nonsecret in composition. These exceptions, therefore, are noteworthy. Since each product is advertised in the catalogue under claims which seemed questionable, regardless of the composition of the preparation, a specimen each of "Modified Salicylic Acid Tablets" and "Samarin Tablets" was obtained and each was examined in the Association's Laboratory.

MODIFIED SALICYLIC ACID

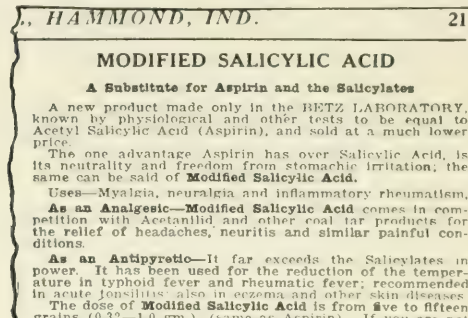
The tablets of modified salicylic acid were labeled: "Tablets Modified Salicylic Acid 5 Gr. Each tablet contains 4 grs. Acid Salicylic so treated as to render it nonirritating to the stomach." The following statements concerning the product are found in the Betz catalogue:

"A Substitute for Aspirin and the Salicylates.

"A new product made only in the Betz Laboratory, known by physiological and other tests to be equal to Acetyl Salicylic Acid (Aspirin), and sold at a much lower price.

"The one advantage Aspirin has over Salicylic Acid, is its neutrality and freedom from stomachic irritation; the same can be said of Modified Salicylic Acid.

"Uses—Myalgia, neuralgia and inflammatory rheumatism.



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MODIFIED SALICYLIC ACID

A Substitute for Aspirin and the Salicylates

A new product made only in the BETZ LABORATORY, known by physiological and other tests to be equal to Acetyl Salicylic Acid (Aspirin), and sold at a much lower price.

The one advantage Aspirin has over Salicylic Acid, is its neutrality and freedom from stomachic irritation; the same can be said of **Modified Salicylic Acid.**

Uses—Myalgia, neuralgia and inflammatory rheumatism.

As an Analgesic—Modified Salicylic Acid comes in competition with Acetanilid and other coal tar products for the relief of headaches, neuritis and similar painful conditions.

As an Antipyretic—It far exceeds the Salicylates in power. It has been used for the reduction of the temperature in typhoid fever and rheumatic fever; recommended in acute tonsilitis; also in eczema and other skin diseases.

The dose of **Modified Salicylic Acid** is from five to fifteen grains (0.32—1.0 gm.), (same as Aspirin). If you are not satisfied with results, we will take back any unused portion and refund your money.

In writing orders or presciptions just say, **"Modified Sal. Acid."**

Prices:

Five Grain Tablets, per M	**$1.65**
Three Grain Tablets, per M	**1.35**
Powder, per oz.	**.20**

A reduced reproduction of the description in the Betz pharmaceutical catalogue of "Modified Salicylic Acid." The Association's chemists found that the product is essentially acetylsalicylic acid (aspirin) with gypsum, starch and talc.

"An an Analgesic—Modified Salicylic Acid comes in competition with Acetanilid and other coal tar products, for the relief of headaches, neuritis and similar painful conditions.

"As an Antipyretic—It far exceeds the Salicylates in power. It has been used for the reduction of the temperature in typhoid fever and rheumatic fever; recommended in acute tonsilitis; also in eczema and other skin diseases.

"The dose of Modified Salicylic Acid is from five to fifteen grains (0.32—1.0 gm.), (same as Aspirin)."

The average weight of ten of the tablets was 0.3843 gm., or about 5.9 grains. Qualitative tests indicated the presence of acetylsalicylic acid (aspirin), calcium sulphate (gypsum), starch, and an acid-insoluble, incombustible substance which

was probably talc. The composition of the tablets was found to be essentially as follows:

Acetylsalicylic acid	81.5 per cent.
Calcium sulphate (gypsum)	9.2 per cent.
Talc (acid insoluble)	0.7 per cent.
Starch (by difference)	8.6 per cent.

Each tablet of "Modified Salicylic Acid" contains, therefore, about 4.8 grains of acetylsalicylic acid and about half a grain each of gypsum and starch with a trace of talc. In other words the product essentially is aspirin. Calcium sulphate, either as gypsum or plaster of Paris, has no use in internal medicine. Neither has it any legitimate place in the manufacture of tablets. Its presence in "Modified Salicylic Acid," therefore, is entirely unjustified either by therapeutic or pharmaceutic necessity. There is nothing in this "new product made only in the Betz Laboratory" to warrant the secrecy under which it is sold, nor the extravagant claims which are made for it. Physicians who desire to prescribe acetylsalicylic acid will find several brands of unquestionable purity from reputable manufacturers described in New and Nonofficial Remedies.

SAMARIN

The following statements concerning Samarin are made on the label of the preparation:

"Properties: Analgesic, Anti-pyretic, Sedative, Antirheumatic, Antifermentative and Anti-lithic, freely soluble, tolerated by the most delicate stomach.

"Uses: In all febrile, painful and uric acid affections, particularly indicated in all neuralgic conditions, insomnia and inflammatory conditions of the respiratory tract.

"Dose—One to three tablets of Samarin, repeated every two or three hours as indicated, not to exceed twelve tablets a day.

"Samarin will give almost immediate relief of severe pain without depression, nausea, or constipation. As a uric acid eliminant it is preferable to the Salicylates, as it causes no stomachic or renal irritation. It is a prompt Analgesic and Sedative, and extensively employed in the treatment of Grippe, Tonsillitis, Acute Bronchitis, Rheumatism and Lithemic Headaches."

The Samarin tablets examined were uncoated and were dyed green throughout. The average weight of ten tablets was 0.35972 gm., or about 5½ grains. Qualitative tests indicated the absence of pyramidon, acetphenetidin, acetylsalicylic acid, free salicylic acid, caffein and other alkaloids, lithium salts and sodium bicarbonate. Tests were obtained for acetanilid, a salicylate, calcium, a sulphate, an acid insoluble, incombustible substance which was probably talc, starch, and a green dye which was not identified.

The analysis indicated the composition of the tablets to be essentially as follows:

Acetanilid	37 per cent.
Calcium salicylate	32 per cent.
Calcium sulphate (gypsum)	7 per cent.
Talc (acid-insoluble)	6 per cent.
Starch and coloring (by difference)	18 per cent.

The analysis of Samarin tablets shows that, when stripped of secrecy, misrepresentations and advertising bombast, the preparation is essentially a mixture of acetanilid with a

SAMARIN

Five Grain Tablets

Properties: Analgetic, Anti-pyretic, Sedative, Anti-rheumatic, Anti-fermentative and Anti-lithic.

Uses: In all febrile, painful and uric acid affections, in neuralgic conditions; insomnia and inflammatory conditions of the respiratory tract.

Samarin will give relief of severe pain without depression, nausea, or constipation. As a uric acid eliminant it is preferable to the Salicylates as it causes no stomachic or renal irritation. It is a prompt Analgetic and Sedative and employed in the treatment of Grippe, Tonsilitis, Acute Bronchitis, Rheumatism and Lithemic Headaches.

In bottles of 1000

7P7545. Bottles of 250, **$0.70**; 1000.....**$3.00**

A reduced reproduction of the description in the Betz catalogue of "Samarin." The Association's chemists reported that this preparation is a mixture of acetanilid and a salicylate. The label on Samarin failed to declare the presence or amount of acetanilid as the Federal law requires.

salicylate. The salicylate found is equivalent to about 25 per cent. of free salicylic acid. Each tablet is equivalent to about 2 grains of acetanilid and nearly 1½ grains of salicylic acid. The presence of acetanilid is not declared on the label of the mixture as is required by law. Physicians know that acetanilid is not a safe drug to prescribe in unlimited doses. That the Frank S. Betz Co. is aware of the unsafe character of Samarin is evidenced by the warning on the label not to take more than twelve tablets in a day. Yet the physician who prescribes Samarin does not know that he is giving either acetanilid or a salicylate.

Details of Analysis

MODIFIED SALICYLIC ACID

Ten of the tablets were weighed singly. The average weight of the tablets was 0.38434 gm., or 5.93 grains.

Chloroform Soluble.—A weighed quantity of the powdered tablets was percolated with chloroform until extraction was

complete, the solvent allowed to evaporate spontaneously, the residue dried over sulphuric acid and weighed. From 0.4714 gm. of material a chloroform-soluble residue of 0.3849 gm. was obtained, equivalent to 81.65 per cent. of the weight taken. A duplicate of 0.5114 gm. gave 0.4095 gm. of chloroform-soluble material, or 81.26 per cent.: Average 81.45 per cent. of chloroform-soluble substance.

Chloroform Insoluble.—The residue insoluble in chloroform was dried in the air, then over sulphuric acid and weighed. From 0.4714 gm. of material 0.0837 gm. of insoluble residue was obtained, equivalent to 17.75 per cent. A duplicate of 0.5114 gm. gave 0.0900 gm. of insoluble material, or 17.60 per cent. Average 17.68 per cent. of chloroform-insoluble material.

Acetylsalicylic Acid.—The chloroform-soluble portion resembled acetylsalicylic acid. A small portion was boiled with water. The odor of acetic acid became noticeable and the solution after cooling gave a violet color with ferric chlorid solution. The melting point of the chloroform-soluble portion was 132-134 C. After mixing with an equal weight of known acetylsalicylic acid the mixture melted at 132-3 C. From these tests it was concluded that the chloroform-soluble portion consisted of acetylsalicylic acid.

Talc.—A weighed portion of the original material was boiled with very dilute hydrochloric acid to decompose acetylsalicylic acid, dissolve calcium sulphate and hydrolyze the starch. The insoluble material was collected in a weighed Gooch crucible, dried, heated nearly to redness, cooled and weighed. From 2.0621 gm. of material 0.0134 gm. of insoluble material was obtained, equivalent to 0.65 per cent. A duplicate of 1.1145 gm. of material gave 0.0080 gm. of insoluble material, or 0.717 per cent. Average, 0.683 per cent. of insoluble material. This had the physical properties of talc.

Calcium Sulphate.—The filtrate from which the talc had been removed was treated with ammonium oxalate solution, the mixture heated and ammonia water added. The precipitate was dissolved in dilute hydrochloric acid and the calcium reprecipitated as oxalate in the usual way. The precipitate was collecetd in a weighed Gooch crucible, dried, heated to form calcium carbonate and weighed as such. The calcium carbonate was calculated to hydrated calcium sulphate. From 2.0621 gm. of material, 0.1083 gm. of calcium carbonate was obtained, equivalent to 9.03 per cent. of hydrated calcium sulphate. A duplicate of 1.1145 gm. of material gave 0.0589 gm. of calcium carbonate, equivalent to

9.09 per cent. of hydrated calcium sulphate. Average 9.06 per cent. of hydrated calcium sulphate, $CaSO_4+2H_2O$. Calcium sulphate was also determined by the barium sulphate precipitation method. The filtrate from the first precipitation of calcium oxalate was added to that from the second precipitation (reprecipitation), the solution heated and acidified with hydrochloric acid. Barium chloride was added and the precipitate collected and weighed in the usual way. From 2.0621 gm. of material 0.2601 gm. of barium sulphate was obtained, equivalent to 9.30 per cent. of hydrated calcium sulphate. A duplicate of 1.1145 gm. of material gave 0.1403 gm. of barium sulphate, equivalent to 9.28 per cent. of hydrated calcium sulphate. Average, 9.29 per cent. of hydrated calcium sulphate, $CaSO_4+2H_2O$.

Starch.—This was determined by difference by subtracting the sum of the acetylsalicylic acid, talc and calcium sulphate from 100. The mean value obtained was 8.59 per cent. Starch was identified by the iodin reaction with and without the aid of the microscope.

SAMARIN

Average weight of Tablets.—Ten of the tablets were weighed singly. The average weight was 0.35972 gm., or about 5.55 grains.

Acetanilid.—A considerable quantity of the tablets was pulverized in a mortar and the powder passed through a No. 60 sieve. A weighed quantity of the powder was percolated with chloroform until extraction was complete, the insoluble residue dried at 100 C. and weighed. A weight of 1.019 gm. gave a chloroform-insoluble residue of 0.578 gm., equivalent to 56.72 per cent. A duplicate of 1.1062 gm. gave 0.6234 of chloroform-insoluble material, equivalent to 56.35 per cent. The chloroform extract from the tablets was washed with water containing a trace of ammonia to remove traces of free salicylic acid or salicylates, the chloroform filtered, evaporated at room temperature by means of a fan, the residue dried over sulphuric acid and weighed. The substance was recrystallized once from water. The recrystallized substance melted at 113-114 C. It gave the isonitrile reaction, but the saturated, aqueous solution gave no precipitate with picric acid solution, silver nitrate test solution, or with mercuric chlorid solution after acidification with hydrochloric acid. The aqueous solution gave a white, crystalline precipitate with bromin solution. The bromin compound was crystallized once from 50 per cent. alcohol, after which it melted at 164 C. Under the same conditions a specimen known to be acetanilid gave a bromin compound which melted between 164

and 165 C. A table of the properties and reactions of acetanilid, acetphenetidin, antipyrin and amidopyrin (pyramidon) was prepared. The substance gave the reactions for acetanilid but not those for acetphenetidin, antipyrin or amidopyrin (pyramidon). The table is given herewith:

REACTIONS OF SOME ANALGESIC SUBSTANCES

	Acetanilid	Acetphenetidin	Antipyrin	Amidopyrin
M. P.	112-114	133-135	111-113	108
Solubility in water	190	1,310	1	11
Isonitrile reaction	Positive	Negative	Negative	Negative
Reaction with bromin.	White ppt. (cryst.) m. p. 164-166	None	Yellowish white	Pale violet color
Ferric chlorid reaction	No color	No color	Red color	Bluish violet
Picric acid	No reaction	No reaction	Yellow ppt.	Yellow ppt.
Silver nitrate	No change	No change	No change	Violet color black ppt.
Mercuric chlorid + HCl	No reaction	No reaction	White ppt.	White cryst. ppt.
Boric acid test	Yellow res. sweet clover odor	Yellowish residue	Naphthalene odor; pink residue	No odor

From 1.019 gm. of material, a weight of 0.3795 gm. of acetanilid was obtained, equivalent to 37.24 per cent. A duplicate of 1.0893 gm. gave 0.4077 gm. of acetanilid, equivalent to 37.43 per cent. Average, 37.33 per cent. of acetanilid.

Salicylic Acid and Calcium Salicylate.—Calcium salicylate was determined by calculation from the amount of salicylic acid found. Also the calcium salicylate was independently calculated from the amount of calcium remaining after deduction of the calcium present as calcium sulphate, from the total calcium. The slightly alkaline, aqueous washings from the chloroformic solution of acetanilid were acidified with hydrochloric acid and the chloroform-insoluble material was treated with this solution together with more warm, very dilute, hydrochloric acid to remove calcium sulphate, to liberate salicylic acid from its combination, and to partially hydrolyze the starch. The cooled solution was extracted with small portions of ether until extraction was complete, the solvent washed with water, evaporated to dryness and the residue dried over sulphuric acid. From 1.019 gm. of material a weight of 0.255 gm. of salicylic acid was obtained, equivalent to 25.02 per cent. of salicylic acid. This is equivalent to 31.73 per cent. of hydrated calcium salicylate

$Ca(C_7H_5O_3)_2+2H_2O$. A duplicate of 1.0893 gm. of material gave 0.2728 gm. of salicylic acid or 25.05 per cent. This is equivalent to 31.77 per cent. of hydrated calcium salicylate.

Acid-Insoluble Substance.—A weighed quantity of the material was incinerated, the residue treated with hot, very dilute hydrochloric acid, the insoluble material collected in a weighed Gooch crucible, heated at low redness, cooled and weighed. The acid-insoluble material appeared to be talc. From 4.0585 gm. of material a weight of 0.2390 gm. of acid-insoluble ash was obtained, equivalent to 5.88 per cent. In another determination 0.7264 gm. of material gave 0.0414 gm. of acid-insoluble material, or 5.70 per cent. Average, 5.79 per cent.

Calcium.—The solution obtained by heating the ash with dilute hydrochloric acid was heated, nearly to boiling, ammonia water added to alkaline reaction and ammonium oxalate solution added in excess. The precipitate of calcium oxalate was dissolved in hydrochloric acid, reprecipitated in the usual way, the second precipitate collected in a Gooch crucible, dried, heated at a temperature below redness and the residue weighed as calcium carbonate. From 4.0585 gm. of material 0.4795 gm. of calcium carbonate was obtained, equivalent to 4.73 per cent. of calcium. In another determination 0.7264 gm. of material gave 0.0837 gm. of calcium carbonate, equivalent to 4.62 per cent. of calcium. Average, 4.67 per cent. of calcium.

Sulphate.—The solution from which the calcium oxalate had been precipitated was acidified with hydrochloric acid, the solution heated nearly to boiling, barium chlorid test solution added and the precipitate of barium sulphate collected, heated and weighed with the usual precautions. From 4.0585 gm. of material 0.4103 gm. of barium sulphate was obtained. This is equivalent to 7.45 per cent. of hydrated calcium sulphate, or 1.73 per cent. of calcium. In another determination 0.7264 gm. of material gave 0.0645 gm. of barium sulphate, equivalent to 6.55 per cent. of hydrated calcium sulphate, or 1.53 per cent. of calcium. Average 1.63 per cent. of calcium. 4.57 per cent. of calcium — 1.63 per cent. of calcium = 2.94 per cent. of calcium above that demanded to combine with all of the sulphate present. 2.94 per cent. of calcium = 25.69 per cent. of calcium salicylate.

Starch.—Starch was determined by substracting the sum of the acetanilid, calcium salicylate, calcium sulphate and talc from 100. The mean value found was 18 per cent. Starch was identified by the iodin reaction with and without the aid of the microscope.

NATIONAL IODINE SOLUTION

(Modified, with additions, from The Journal A. M. A., June 4, 1921, p. 1592)

"National Iodine Solution" is a proprietary sold by the National Drug Co., Philadelphia, Pa. From inquiries received by the Council on Pharmacy and Chemistry it is evident that the product is extensively brought to the attention of physicians by means of circulars. The name implies that it is a solution of iodin and the inference is given that it has the advantages of iodin without the disadvantages.

In view of the foregoing, the Council took up the investigation of "National Iodine Solution," and in turn asked the A. M. A. Chemical Laboratory to analyze it.

LABORATORY REPORT

According to the label of National Iodine Solution, "each fluidounce represents three grains Proteo-albuminoid compound of iodine (National)"; also an alcohol declaration of 7 per cent. is made. Otherwise no information is given as to the composition either of the "solution" or of "Proteo-albuminoid compound of iodine."

Each bottle contained about 115 c.c. (nearly 4 ounces) of a yellowish solution, acid in reaction, having an odor resembling witch hazel; its specific gravity at 25 C. was 0.9860. Qualitative tests indicated the presence of zinc, alcohol, sulphate, an iodin compound (the solution gave tests which indicated a very small amount of free iodin; most of the iodin was in the form of ordinary iodid), a small amount of vegetable extractives, and traces of aluminum and potassium. If any protein was present, it was in amounts too small to be identified, though a small amount of a nitrogenous compound was present. The amount of solids in "National Iodine Solution" was equivalent to 0.72 per cent. and the amount of ash, to 0.2 per cent. Quantitative estimations yielded the following:

Alcohol (by volume)	7.0 per cent.
Zinc (Zn^{++})	0.096 per cent.
Iodin (free and combined)	0.029 per cent.
Sulphate (SO_4^{--})	0.147 per cent.
Protein (N × 6.36)	0.012 per cent.

The above findings indicate that each 100 c.c. contains about 7 c.c. of alcohol, 0.5 gm. of zinc sulphate U. S. P. ($ZnSO_4+7H_2O$), 0.03 gm. of iodin, 0.01 gm. of protein

(calculated as such from nitrogen times the factor 6.36) and some hamamelis water. Expressed in equivalent apothecary terms, each fluidounce contains essentially:

Zinc sulphate	2⅓ grains
Iodin (free and combined)	⅛ grain
Protein	1/26 grain
Alcohol	34 minims

This amount of alcohol is equivalent to about 3½ fluidrams of witch hazel water. Although the label states that each fluidounce contains three grains of "proteo-albuminoid compound of iodine," yet the sum of the protein (calculated from nitrogen content) and iodin components is equivalent to less than ⅓ grain.

"National Iodine Solution" appears to be very similar to "Gonocol (The National Drug Co., Philadelphia, Pa.)," which was analyzed by the bureau of Chemistry of the U. S. Department of Agriculture. The bureau stated that "it [Gonocol] consisted essentially of an aqueous solution of zinc sulphate, hamamelis water, a small amount of alcohol, 0.38 grain of iodin, and 0.36 grain of protein per fluidounce."

It is evident that "National Iodine Solution" is not a solution of free (elementary) iodin as the name suggests; instead it appears to be a solution of zinc sulphate in witch hazel water containing less than 0.03 per cent. of combined iodin and *not more than a trace of free iodin.* "National Iodine Solution" is one more to be added to that already long list of proprietaries which makes capital of the high esteem in which physicians hold iodin.

In its report, the Council on Pharmacy and Chemistry made the following comment:

"It is of interest to note that the claims for an identical or a similar solution prepared by the National Drug Company as a treatment for gonorrhea and intended for use by the laity, has been adjudged misbranded by the federal authorities (Notice of Judgment No. 8150, issued Jan. 25, 1921) in that it misled and deceived the purchaser or purchasers thereof in the statements regarding the therapeutic or curative effects of the article, which falsely and fraudulently represent it to be indicated in all conditions of the urethra accompanied with a discharge, 'whereas in truth and in fact it was not.'

"The Council would emphasize that if physicians give heed to advertising such as that sent out by the National Drug

Company for this preparation the medical profession cannot with good grace protest against the routine treatment of venereal diseases by quacks and 'patent medicine' venders."

Details of Analysis

Solids and Ash.—Fifty c.c. of the original material were placed in a weighed platinum dish, the solution evaporated over a steam bath and the residue dried for 12 hours at 120 C. The residue weighed 0.3598 gm., equivalent to 0.72 per cent of solids. The dish and contents were then heated over a free flame until the carbon was consumed. The weight of ash was 0.1001 gm., equivalent to 0.2 per cent.

Alcohol.—One hundred c.c. of the original material were placed in a distillation flask and 50 c.c. of water added. The alcohol was distilled over, using apparatus described in U. S. P. IX, p. 592, until the distillate measured almost 100 c.c. (The residue was used for determination of the zinc.) Sufficient water was added until the distillate measured exactly 100 c.c., and the specific gravity of the distillate determined at 25 C. Sp. Gr. = .98987 = 7.00 per cent. of alcohol by volume.

Zinc.—The residue from the alcohol determination was filtered (to remove substance previously held in solution by the alcohol), and with washings, made up to 100 c.c. An aliquot portion was used for the determination of zinc as zinc ammonium phosphate, $ZnNH_4PO_4$ according to the method described in Analytical Chemistry, Treadwell-Hall, Vol. II (1915) page 140. (a) Fifty c.c. yielded 0.0128 gm. of zinc ammonium phosphate, $ZnNH_4PO_4$, equivalent to 0.0941 gm. of Zn, or 0.095 per cent. (b) 50 c.c. yielded 0.1306 gm. of the zinc salt $ZnNH_4PO_4$, equivalent to 0.0950 gm. of Zn or 0.096 per cent.

Iodin.—There was only the slightest coloration in the chloroform layer after the solution was shaken with chloroform; acidification with dilute hydrochloric acid made no perceptible change. Addition of ferric chlorid solution did not seem to increase the amount of free iodin, but nitric acid did. Silver nitrate precipitated all of the iodin, as the filtrate, after treatment with fuming nitric acid in a closed tube, yielded no precipitate. Chlorids and bromids were absent. Hence the iodin was determined by precipitation with silver nitrate solution, acidification with nitric acid, and boiling. (a) Fifty c.c. of the original yielded 0.0262 gm. of silver iodid, equivalent to 0.028 per cent. of iodin. (b) Fifty c.c. yielded 0.0287 gm. of silver iodid, equivalent to 0.030 per cent. of iodin (I).

Sulphate.—Sulphate was determined by precipitation with barium chlorid in presence of hydrochloric acid. (a) Twenty-five c.c. of the original material yielded 0.0887 gm. of barium sulphate ($BaSO_4$), equivalent to 0.147 per cent. of sulphate ion (SO_4^{--}); (b) Twenty-five c.c. yielded 0.089 gm. of barium sulphate, equivalent to 0.148 per cent. of sulphate ion (SO_4^{--}).

Protein (Nitrogen Times Factor 6.36)—The nitrogen content was determined according to the method for "Total Nitrogen in Urine," Medical War Manual No. 6, Laboratory methods of the United States Army, 2nd Edition, p. 221. (a) Fifty c.c. of the original after digestion yielded ammonia sufficient to neutralize 0.75 c.c. of tenth-normal hydrochloric acid, equivalent to 0.0134 per cent. of protein. (b) Fifty c.c. of the original after digestion yielded ammonia sufficient to neutralize 0.65 c.c. of tenth-normal hydrochloric acid, equivalent to 0.0116 per cent. of protein.

REOLO

(Abstracted from The Journal A. M. A., June 11, 1921, p. 1697)

Several inquiries have been received regarding "Reolo" of the "Dr. A. L. Reusing Laboratories," Akron, Ohio. The advertising matter of Reolo bears the earmarks of another attempt to capitalize what certain "patent medicine" concerns have called the "Biochemic Treatment." This "treament" is based on the theory—which has no scientific basis—that all disease is the result of a variation in the inorganic salt-content of the cells. Starting with this hypothesis, it is argued that all that is necessary for the treatment of any disease is to make good the salt deficiency of the cells. This is done by administering tablets alleged to contain certain salts in infinitesimal amounts. Examination of the medicaments used by the exponents of this theory usually discloses nothing more potent in the tablets than milk sugar or something equally innocuous.

Some of the claims made in the Reolo advertising are:

"All diseases that are curable are cured in a natural way through the circulation of the blood which is carried by the blood vessels, and transudes through the walls of the veins and capillaries into the surrounding tissues. When the blood contains the proper amount of Cell-Salts and Red Blood Cells the whole body glows with health and vitality the eyes sparkle sleep is refreshing and you are free from aches and pains."

"The treatment of disease with Cell-Salt is so rational and in such perfect accord with the well-known principles of Nature's laws, that it is only necessary to explain its basic principle and any intelligent person will instantly admit that it is the only natural, scientific treatment for disease."

"The world's most eminent physicians have conducted exhaustive laboratory tests in an endeavor to obtain a perfect combination of these Cell-Salts that will be promptly assimilated by the cells of the body."

"Dr. A. L. Reusing has finally succeeded in combining by electrical treatment the phosphates of calcium, sodium and iron with the phosphates of potassium and magnesium, and has obtained a perfect combination of these revitalizing Cell-Salts that he has named 'Reolo,' which produces a very rapid increase in the number of red blood cells and a greater percentage of hemoglobin in the blood."

Reolo was submitted to the A. M. A. Chemical Laboratory for examination and the following report published in THE JOURNAL:

"The specimens of Reolo examined consisted of greyish-brown tablets having a sweet, chocolate-like and faintly bitter taste. Iodids, bromids, emodin-bearing (laxative) drugs, arsenic, salicylates and sulphates were absent. Alkaloids were absent or present, if at all, only in traces. Very small quantities of a phosphate and traces of magnesium were present. Large amounts of calcium carbonate (chalk) and sucrose (cane sugar) were present; also traces of an iron compound. The substance imparting the bitter taste was not identified. The tablets do not appear to be medicated in the usually accepted sense."

THE JOURNAL commented on the composition of Reolo as follows:

"From this it would appear that 'Reolo, The Health Renewer,' is essentially a mixture of cane sugar and chalk!"

IODINOL

An "Intensified Iodin" at an Intensified Price

(Reprinted, with additions, from The Journal A. M. A., Aug. 20, 1921, p. 637)

Although reports on the composition and therapeutic efficiency of several of the so-called "organic iodin" preparations have been published,[1] THE JOURNAL still continues to receive inquiries concerning products of this type. In view of the general interest in the subject it, seemed worth while

1. Iodalin: J. A. M. A., Dec. 12, 1914, p. 2149. Nourry Wine, J. A. M. A., Dec. 12, 1914, p. 2150.

to examine "Iodinol," another member of this class. Iodinol is put out by the Toledo Pharmacal Co.; price to physicians: one dollar a pint. Concerning its composition, the manufacturer states that Iodinol is:

> A water solution of organic iodin containing one grain of the element in each fluidrachm.

The circular describing Iodinol refers to the preparation as "intensified iodin"—whatever that may mean—but no information is offered concerning the nature of the "organic iodin" compound in Iodinol. Hence, the product is essentially secret in composition. In order to determine the character of the iodin in Iodinol, a specimen of the product was examined in the A. M. A. Chemical Laoratory and the following report published in THE JOURNAL:

"Iodinol is of the consistency of thin syrup, has a brown color and a peculiar, not unpleasant odor, resembling that of the official syrup of ferrous iodid. The reaction is strongly acid to litmus. On evaporation and subsequent ignition of the residue, the preparation leaves almost no ash. Reducing sugars are present in large amounts. The preparation darkens on the addition of ferric chlorid solution, thus indicating the presence of tannin. The absence of uncombined iodin is demonstrated by the fact that when chloroform is added to the preparation and the mixture shaken no violet color is produced in the chloroform layer. By adding ferric chlorid solution and shaking with chloroform, a violet color results. The addition of an excess of silver nitrate solution to a dilute aqueous solution of Iodinol immediately produces a precipitate of silver iodid. The dilute solution gives a yellow precipitate with lead acetate solution and a scarlet precipitate with mercuric chlorid solution. These tests indicate that the iodin in Iodinol exists in some combination which is as readily ionized as potassium iodid. After the precipitate with silver nitrate has been removed by filtration, the excess of silver removed by the addition of hydrochloric acid and a second filtration, the clear filtrate does not respond to tests for any form of iodin. These tests demonstrate that all of the iodin contained in Iodinol is present either in the form of iodid ions or in a combination which readily yields iodid ions.

"In a true 'organic iodid' compound, the iodid is so closely bound in the molecule that it cannot be precipitated directly as an iodid by the soluble silver salts. Such a compound (or its decomposition products) is relatively more slowly absorbed in the organism than are the metallic iodids, and it is correspondingly less irritating to the digestive tract.

Since all of the iodin in Iodinol is readily precipitated by silver nitrate solution, it is obvious that it can not be considered an 'organic iodin' preparation, either from the chemical or the therapeutic viewpoints.

"Quantitative determinations of the combined iodin in the specimen indicates that Iodinol contains about 1.708 gm. of iodin per 100 c.c., or about 7.78 grains per fluidounce. This is essentially the claimed iodin content (1 grain per fluidrachm or 8 grains per fluidounce).

"The examination indicates that Iodinol is an iodo-tannic preparation, probably similar to the iodo-tannic syrup official in the French Pharmacopeia, except that it is stronger in iodin than the French preparation."

Concerning the exploitation of Iodinol THE JOURNAL commented as follows:

A correspondent writes to THE JOURNAL:

The reason I have been using Iodinol is because it is a *relatively cheap and convenient way to dispense iodin for internal use.* I don't regard it as unethical, since the Council has failed to suggest a suitable substitute.

Iodinol is *not* "a relatively cheap . . . way to dispense iodin." Iodin in the form of Iodinol is about fourteen times more expensive than when purchased in the form of potassium iodid, and ten times as expensive per iodin unit, as sodium iodid. Furthermore, the Council has *not* failed to suggest a suitable substitute. The following true "organic iodin" preparations are described in New and Nonofficial Remedies:

	Per Cent. of Iodin
Iodalbin	21.5
Iodocasein	18.0
Iodoleine	26.0
Iodoleine	33.0
Lipoiodine—"Ciba"	41.0
Riodine	17.0
Sajodin	24.5

There is no secrecy about any of these iodin compounds and the physician may prescribe any of them with the expectancy of obtaining iodin effects. The results may be somewhat slower to appear in organic iodin therapy than by treatment with a soluble metallic iodid, owing to slower absorption, but the aggregate effects are identical under either form of treatment.

Concerning the results from the use of inorganic iodids, such as potassium iodid, the manufacturer of Iodinol states:

A destruction of the tubules of the kidneys may take place, nervous symptoms may develop and in a great many cases the heart becomes affected.

There is no creditable pharmacologic evidence to indicate that the administration of the inorganic iodids causes "a destruction of the tubules of the kidneys." The "nervous symptoms" and tachycardia usually occur in persons with thyroid dysfunction and do not take place "in a great many cases" as the Iodinol exploiters assert. Further, there is no evidence that iodism is less apt to occur after the use of organic combinations of iodin than after the administration of inorganic iodids of equivalent iodin dosage. In those instances in which iodism has followed the administration of potassium iodid and in which equivalent symptoms did not occur after treatment with iodin in organic combination, it has usually been shown that the iodin dosage was much lower in the latter cases than in the former.

The label for Iodinol states:

Iodinol in teaspoonful doses is equal in therapeutic action to 10 and 15 grains of potassium iodid with the minimum systemic disturbance.

This statement is absurd. "Ten to fifteen grains of potassium iodid" are equivalent to from seven and a half to eleven grains of iodin while one fluidrachm of Iodinol contains *less than one grain of iodin!* Discriminating clinicians and pharmacologists hold that, if a given quantity of iodin be administered in an absorbable form, it will produce essentially the same effects regardless of whether it be given as "inorganic" or as "organic" iodin.

Therapeutically, Iodinol is no better than a sweetened solution of potassium iodid of equivalent iodin content; economically, it is far more expensive than potassium iodid or the other official iodids; ethically, it is to be condemned because it is secret in composition and is sold under exaggerated, unwarranted and untruthful claims.

Details of Analysis

Ash.—On evaporation Iodinol leaves considerable residue but on heating this only traces of ash remain. This demonstrates the absence of metallic iodids such as potassium iodid or sodium iodid, purgative salts, such as Glauber's salt or Epsom salt, iron salts, phosphates and the salts of the heavy metals (except mercury).

Ammonium salts, sulphates and mercury salts were absent. Reducing sugars, tannic acid and iodin in the form of iodid ions, were present in considerable amounts.

Iodin.—A portion of the material was diluted with water and shaken with chloroform. No color in the chloroform layer resulted. A few drops of chlorin water were added and the mixture again shaken. The chloroform layer became violet. The test was repeated using sodium nitrite solution instead of chlorin water. The result was identical with that obtained with chlorin water. An aqueous soluion of berberin hydrochlorid gave a yellow precipiate with a diluted aqueous solution of Iodinol. As noted in the published report of the Laboratory, the diluted solution of Iodinol gave a pale yellow precipiate with silver nitrate solution, a yellow precipitate with lead acetate solution and a scarlet precipitate with mercuric chlorid solution. These tests demonstrate that the iodin in Iodinol exists in a form which is readily ionizable. A portion of the warmed, diluted material was treated with an excess of silver nitrate solution, the precipitate removed by filtration, a slight excess of hydrochloric acid added to precipitate the excess of silver, the precipitate of silver chlorid removed by filtration, the filtrate evaporated to dryness and the residue fused with a mixture of sodium carbonate and sodium hydroxid. The fused mass was cooled, dissolved in water, a slight excess of hydrochloric acid added (in small portions) and a few drops of sodium nitrite solution added. On shaking with chloroform no violet color resulted in the chloroform layer. This test demonstrates that all of the iodin in Iodinol is precipitable by silver nitrate solution.

For the quantitative determination of the iodid ions, an excess of silver nitrate solution was added, the silver iodid collected, dried and weighed in the usual way. The silver iodid from 10 c.c. of the material weighed 0.3157 gm., equivalent to 0.17057 gm. of iodin, or 1.706 gm. per 100 c.c. A duplicate gave 0.3167 gm. of silver iodid, equivalent to 0.17111 gm. of iodin, or 1.711 gm. per 100 c.c. Average, 1.71 gm. of iodin per 100 c.c.

Tannin.—A portion of the original material darkened on the addition of ferric chlorid solution. A solution of quinin hydrochlorid was added to a portion of the material. A flocculent precipitate formed on standing. A portion of the material was allowed to stand over night in contact with calcium carbonate (calc spar) to neutralize the free acids. The solution was saturated with sodium chlorid and shaken with ethyl acetate. The solvent was washed with saturated sodium chlorid solution and evaporated to dryness on the steam bath. The residue was taken up in water. A portion of the solution gave an intensely blue-black color with ferric

chlorid solution. Another portion gave a flocculent precipitate with quinin hydrochlorid. Another portion precipitated an aqueous solution of gelatin. These tests were considered as demonstrating the presence of tannic acid in Iodinol.

MAGHEE'S EPILEPSY TREATMENT

(Abstracted, with additions, from The Journal A. M. A., Sept. 24, 1921, p. 1057)

During the past year THE JOURNAL has received inquiries regarding an alleged remedy for epilepsy sold on the mail-order plan by Thomas G. Maghee, M.D., of Lander, Wyoming. For instance, a North Carolina physician writes:

"The enclosed card and envelope containing two capsules are self-explanatory. I hope you can inform me concerning this treatment for epilepsy by letter or through THE JOURNAL. (Please omit my name.) What drug is contained in the capsule?"

And this from a physician in Nebraska:

"I am sending, under separate cover, six capsules of some preparation that is used for the treatment of epilepsy by a Dr. Maghee of Lander, Wyoming. Do you know anything about this treatment and will this be a large enough amount for analysis? I have a man here who has been using this for his son."

While this from a layman in Louisiana:

"I herewith attach circular letter on treatment for epilepsy. I would be glad to hear from you if you know anything of this treatment. I have a boy who is about 7 years old who has been suffering from this trouble for about six and one-half years."

Dr. Maghee seems to reach his mail-order clientele through the classified advertising section, of newspapers.

Those who write either to "Specialist, Drawer 592, Lander, Wyoming," or to Thomas G. Maghee, receive a printed letter, in which the sufferer is offered a "treatment which from the first day of its use, according to directions, will relieve you completely from any recurrence of seizures or other symptoms of the dread disease." In addition to the printed letter there is a small eight page leaflet bearing the imprint of "Maghee Chemical Corporation" and entitled "Dr. Maghee's Method of Treatment for the Immediate and Continuous Relief of Epilepsy."

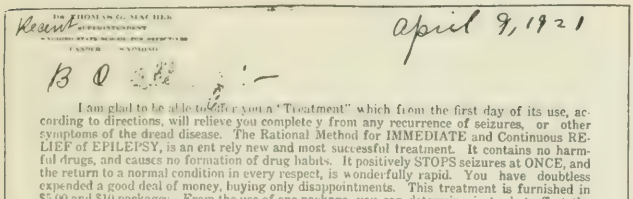
Some of the claims made in this advertising matter are:

"My Rational Method of Treatment of Epilepsy Affords Immediate, Complete, and Continuous Relief From Seizures and all Other Symptoms."

"Seizures will CEASE to occur at once, nervousness will decrease, sleep become normal and refreshing, the complexion will clear up and the MIND WILL IMPROVE RAPIDLY."

"This . . . Treatment . . . has in the five years of its use, prevented more suffering for the unfortunate victims of epilepsy, than the entire medical profession has been able to accomplish, during all the centuries which have rolled by since the practice of medicine began."

It is fairly obvious that the claims emphasized throughout the Maghee advertising matter to the effect that the treatment



April 9, 1921

I am glad to be able to offer you a "Treatment" which from the first day of its use, according to directions, will relieve you completely from any recurrence of seizures, or other symptoms of the dread disease. The Rational Method for IMMEDIATE and Continuous RELIEF of EPILEPSY, is an entirely new and most successful treatment. It contains no harmful drugs, and causes no formation of drug habits. It positively STOPS seizures at ONCE, and the return to a normal condition in every respect, is wonderfully rapid. You have doubtless expended a good deal of money, buying only disappointments. This treatment is furnished in $5.00 and $10 packages. From the use of one package, you can determine just what effect the treatment will have in your case. That you may not in this instance, pay for what you do not get, if you purchase either sized package, use the contents according to directions, and find the results are not exactly what it is represented they will be in this letter, and in the enclosed "Thesis," or are not in every way entirely satisfactory to you, the price you pay for this trial package, will be returned to you, by the next mail after your demand for it is received. This is no idle promise, as under the Postal Law, I would be punishable for fraudulent use of the mails if the promise was not promptly complied with. Can you afford to miss this opportunity to obtain what you have so long fruitlessly sought? This will NOT prove a disappointment. Similar sufferers, in your city and in various parts of The United States, are happily enjoying the great benefits which this treatment affords.

Respectfully,

Thos. H. Maghee

Photographic reproduction (reduced) of the letter sent out in reply to those who answer the Maghee newspaper advertisements. Note the use of the title "Superintendent" with "recent" written before it. "Recent," in this case, means six years ago.

gives "IMMEDIATE and CONTINUOUS RELIEF of EPILEPSY" that it "positively STOPS seizures at ONCE" and that those who take it "return to a normal condition in every respect," can mean but one thing to the public, namely, that this is a cure for epilepsy.

The Maghee treatment comes in $5 and $10 packages. Five dollars was sent to Dr. Maghee with the request that he send a package with full directions. It came in due time and was turned over to the A. M. A. Chemical Laboratory.

LABORATORY REPORT

One original box of "Dr. Maghee's Rational Method of Treatment" for the relief of epilepsy was submitted to the Chemical Laboratory for examination. The box bore the statement: "It contains no bromides, opiates, other narcotics nor other habit forming drugs. . . ." In the box were 40 small sized capsules, containing a powdered mixture of black color; the average contents of each capsule was 0.105 gm. (1.6 grain). Qualitative tests indicated the presence of charcoal ("wood"), bismuth, nitrate and phenobarbital (luminal). The quantitative determinations were as follows:

Moisture (dried at 120 C.)	1.0 per cent.
Bismuth (equivalent to 3.8 per cent. bismuth subnitrate)	2.8 per cent.
Charcoal	31.9 per cent.
Phenobarbital (luminal)	64.5 per cent.

For practical purposes, it may be deduced from the analysis that each capsule contains as its essential ingredient 0.068 gm. (approximately 1 grain) of phenobarbital (luminal) with which has been mixed 0.033 gm. (½ grain) of charcoal and a very small amount of bismuth subnitrate.

In commenting on this nostrum, THE JOURNAL stated:

"The essential drug, then, in Maghee's 'Rational Method for Immediate and Continuous Relief of Epilepsy' is phenobarbital (luminal). Although, from reading Maghee's advertising matter, the public would get the impression that Maghee discovered the value of this drug in epilepsy, the facts are it has been used in epilepsy both in this country and abroad and the results reported on in medical journals for the past nine years.

"Summed up, it may be said that there is no rational excuse for the sale of phenobarbital in a secret mixture sold on the mail order plan for the self-treatment of so serious a condition as epileptic seizures."

Details of Analysis

Due to the small amount of material, it was necessary to make certain qualitative tests on products after the quantitative estimations had been carried out.

Phenobarbital.—After extraction with chloroform in the Soxhlet apparatus, the chloroform extract was evaporated to dryness, and dried at 100 C. for 3 hours. (a) A weight of 0.7054 gm. yielded 0.4580 gm. of extract, equivalent to 65.0 per cent. (b) A weight of 1.0388 gm. yielded 0.6657 gm. of extract, equivalent to 64.0 per cent. of phenobarbital. In one

instance a small portion of extract was powdered and its melting point taken, which was 171-172 C (uncorr.). The melting point of a specimen of "luminal-Winthrop" was 171-172 C. (uncorr.) and a mixture of the two melted at the same temperature. The extract dissolved in dilute sodium hydroxid solution; a precipitate formed when the solution was acidified.

Bismuth.—The residue in the Gooch crucible (which had been treated with hot chloroform in a Soxhlet extraction apparatus, dried and weighed) was treated with hot nitric acid solution 1:1; the filtrate was used for qualitative tests. Bismuth was identified by the formation of a brownish-black precipitate by hydrogen sulphid in acid solution. The precipitate was insoluble in alkali sulphid; it dissolved easily by heating with nitric or hydrochloric acid solutions 1:1. When some of this latter solution was evaporated almost to dryness, then diluted with water, a white precipitate formed ($BiOCl_2$); also when the nitrate was made alkaline, and stannous chlorid in strong potassium hydroxid solution was added, a black precipitate was formed. The quantitative estimation was made according to "Method D" as described by Puckner and Hilpert (The Examination of Bismuth Betanaphtholate, Proceedings A. Ph. A. 1909, vol. lvii; Reports of A. M. A. Chemical Laboratory, vol. 2, 1909, p. 46). A weight of 1.2440 gm. of the powder was treated with 15 to 20 c.c. of hot nitric acid solution 1:1, diluted with a equal volume of water, the solution filtered and the filter washed well with dilute nitric acid. The filtrate after further dilution was made ammoniacal, then slightly acid; the bismuth was precipitated by ammonium phosphate. The bismuth phosphate weighed 0.0516 gm. equivalent to 2.8 per cent. of bismuth (Bi), 3.1 per cent. of bismuth oxid or 3.8 per cent. of bismuth subnitrate U. S. P. (assuming the amount of Bi_2O_3 to be 80 per cent. of the weight of bismuth subnitrate).

Charcoal.—The black material was insoluble in acids or alkalis, 1:1, but was burned easily. Under the microscope it had the characteristics of wood charcoal. It was determined by weighing the residue left after extraction with chloroform in a Soxhlet apparatus, and deducting 3.8 per cent. as bismuth subnitrate. (a) A weight of 0.7054 gm. left a residue weighing 0.2510 gm. equivalent to 31.7 per cent. (the residue in the Gooch crucible was ignited and the ash remaining weighed 0.0588 gm.). (b) A weight of 1.0388 gm. left a residue weighing 0.3719 gm., equivalent to 32.0 per cent. of charcoal.

PIL. MIXED TREATMENT (CHICHESTER)

(Abstracted, with additions from The Journal A. M. A., Oct. 22, 1921, p. 1355)

"Pil. Mixed Treatment (Chichester)" is a proprietary preparation of the Hillside Chemical Co., Newburgh, N. Y., It is sold in the form of pills, each said to contain $\frac{1}{20}$ grain of mercuric iodid and 5 grains of potassium iodid.

In 1907 the Council on Pharmacy and Chemistry of the American Medical Association examined the therapeutic claims advanced for this preparation and found that they were unwarranted, exaggerated and misleading. It found, also, many misleading statements in regard to the product itself. Furthermore, the A. M. A. Chemical Laboratory found the pills to be "short weight" in potassium iodid content.

In 1921 the Council again took up the examination of Pil. Mixed Treatment (Chichester) and the Chemical Laboratory was requested to determine the content of potassium iodid and that of mercuric iodid.

Details of Analysis

Average Weight of Pills.—Twenty pills were weighed in bulk. The whole weighed 14.233 gm., or 0.711615 gm. each. This is equivalent to about 10.98 grains each. Since the pills are claimed to contain but 5 grains of potassium iodid and one-twentieth grain of mercuric iodid, it is evident that some foreign substance must be present in considerable amounts.

Water-Insoluble Ash.—Twenty pills, accurately weighed, were dissolved so far as possible in water by maceration over night and subsequent filtration. The insoluble part was well washed on the filter with distilled water, the washings added to the filtrate and the solution reserved. The insoluble portion was dried and heated at a low red heat to destroy carbonaceous matter. The ash was macerated with water, filtered through a weighed Gooch crucible, the filtrate added to the filtrate and washings reserved above, the Gooch crucible dried, heated and weighed. The water-insoluble ash from 20 pills weighed 2.4765 gm., equivalent to 17.4 per cent. of the original weight. This is equivalent to about 0.12383 gm. for each pill. The aqueous reserved solution (filtrate and washings) was made up to 250 c.c. and aliquot parts taken for various tests and determinations.

Total Iodid.—An aliquot portion of 25 c.c. of the solution above described (representing 2 pills) was slightly acidified

with nitric acid, an excess of silver nitrate solution added, the silver iodid collected, dried and weighed in the usual way. The silver iodid from 25 c.c. of the solution weighed 0.9066 gm., equivalent to 0.489836 gm. of iodin or 34.42 per cent. This is equivalent to 45.04 per cent. of potassium iodid. A duplicate of 25 c.c. gave 0.9065 gm. of silver iodid, equivalent to 0.489782 gm. of iodin, or 34.41 per cent. This is equivalent to 45.03 per cent. of potassium iodid. Average, 34.41 per cent. of total iodid, equivalent to 45.03 per cent. of potassium iodid. This is equivalent to 4.95 grains of potassium iodid per pill. Claim, 5 grains of potassium iodid and $\frac{1}{20}$ grain of mercuric iodid.

Mercury.—Hydrogen sulphid produced no precipitate in the warm, diluted, aqueous solution even on long standing. This is probably due to the very great excess of potassium iodid over the mercuric iodid. Mercury was determined as follows:

> To 100 c.c. of the above described aqueous solution a few drops of nitric acid were added, the solution warmed and a slight excess of silver nitrate solution added. The silver iodid was collected on a filter and washed, the washings being added to the filtrate. The excess silver was precipitated from the filtrate by the addition of a slight excess of sodium chlorid, the precipitate removed by filtration, and washed, the washings being added to the filtrate. A slight excess of ammonia water was added to the filtrate to neutralize the nitric acid, the solution evaporated somewhat to remove excess ammonia and to reduce the volume, hydrogen sulphid was passed in, the precipitate of mercuric sulphid collected in a weighed Gooch crucible, washed with alcohol, then several times with carbon disulphid, dried and weighed.

From 100 c.c. of solution, representing 8 pills, 0.0079 gm. of mercuric sulphid was obtained equivalent to 0.00191625 gm. of mercuric iodid per pill *or 59.1 per cent. of claim.* The aqueous extract from 20 pills gave 0.0206 gm. of mercuric sulphid, equivalent to 0.040238 gm. of mercuric iodid, or 62.08 per cent. of the amount claimed. Average, 60.59 per cent. of the amount of mercuric iodid claimed.

SAL HEPATICA

(Abstracted, with additions, from The Journal A. M. A., Oct. 29, 1921, p. 1438)

Sal Hepatica is a saline laxative sold by the Bristol-Myers Company of New York. Little information is given or, apparently, ever has been given, concerning the composition

of this product. Many years ago the stock medical journal advertisement contained this statement:

"*Composition.*—Sal Hepatica contains all of the Tonic, Alterative and Laxative Salts of the celebrated 'Bitter Waters' of Europe, especially those of Bohemia, as determined by actual chemical analysis of these waters, and fortified by the addition of Lithium and Sodium Phosphates."[1]

Sal Hepatica no longer "contains all the tonic, alterative and laxative salts . . . ," etc., for the label on a package recently purchased reads:

"Sal Hepatica is an effervescent saline combination possessing medicinal properties similar to the natural 'Bitter Waters' of Europe, and fortified by the addition of Sodium Phosphate."

In 1909, the *Druggists Circular* published an analysis of Sal Hepatica which showed that the preparation contained only 0.04 per cent. of lithium phosphate. By referring to the two quotations just given it will be noticed that today the manufacturers make no claim that their preparation is fortified with any salt of lithium. A circular accompanying recent trade packages states:

"Sal Hepatica is composed solely of harmless salts, being absolutely free from Acetanilid, Phenacetin, Caffein, Calomel, opium or coal tar derivatives."

Since neither the names nor the amounts of the "harmless salts" are mentioned, the composition of Sal Hepatica is secret. It is a trick of the nostrum exploiter, old but ever popular, to mention numerous drugs which his preparation does *not* contain; it helps to distract attention from the fact that he does not tell what the preparation *does* contain!

In the old-time medical journal advertisements, one reads: "Sal Hepatica is the most powerful solvent of Uric Acid known." (The same advertisement as it appeared in those days in THE JOURNAL shows that claim toned down to: "Sal Hepatica is a powerful solvent of Uric Acid"). In those easy-going days Bristol-Myers Co. declared that: "Diabetes is treated with decided advantage by means of Sal Hepatica . . . it . . . possesses the property of arresting the secretion of sugar in the liver." In the old days, too, Sal Hepatica was recommended in the treatment of cirrhosis of the liver, Bright's disease, gravel, phthisis, etc.

The present advertising circular recommends Sal Hepatica as an eliminant, laxative or cathartic in Gout, Autointoxica-

1. Some of the Sal Hepatica advertising has claimed that it "is a saline combination with the addition of Sodium Phosphate and *Lithia Citrate!*"

tion, "Bilious Attacks," Rheumatism, Acute Indigestion, Catarrhal conditions of the stomach, Pyorrhea, Headache, Dizziness, Heart Burn, "Summer Complaints," "Derangements of the Stomach and Liver," Skin Diseases, Colic, Alcoholic excesses, and as a "preventive of Seasickness."

In 1914 the Council on Pharmacy and Chemistry published[2] a report on Sal Hepatica declaring it secret in composition and sold under exaggerated and unwarranted claims.

In view of the inquiries which THE JOURNAL continues to receive it seemed worth while to make a chemical examination of the present-day product. Accordingly specimens were purchased, analyzed and the report that follows was published in THE JOURNAL:

"Sal Hepatica is a white, granular, odorless powder. It effervesces on the addition of water in which it eventually dissolves. The aqueous solution, after boiling to remove carbon dioxid, has an acid reaction to litmus.

"Since a great many medicinal substances are sold in effervescent form, and since practically no information is given by the manufacturer concerning the composition of Sal Hepatica, it became necessary to test for a considerable number of therapeutic agents. The absence of acetanilid, acetphenetidin, alkaloids, ammonium salts, benzoates, caffein, citrates, heavy metals, hexamethylenamin, magnesium, potassium, salicylates and sugars was demonstrated by appropriate tests. The presence of a carbonate (probably in the form of a bicarbonate), a phosphate, a sulphate, a chlorid, tartaric acid, sodium and traces of lithium was shown by qualitative tests.

"Quantitative analysis indicated that the composition of the specimens examined was essentially as follows:

Sodium phosphate, anhydrous	4.4 per cent.
Sodium sulphate, anhydrous	26.5 per cent.
Sodium tartrate, anhydrous	12.7 per cent.
Sodium bicarbonate	19.5 per cent.
Tartaric Acid, free	20.8 per cent.
Sodium chlorid	8.9 per cent.
Lithium phosphate	trace
Water of hydration (by difference)	7.2 per cent.

"From the results of the analysis, it appears probable that the composition of the mixture before 'granulation' was approximately as follows:

Sodium phosphate	4 per cent.
Sodium sulphate	25 per cent.
Sodium bicarbonate	30 per cent.
Tartaric Acid	30 per cent.
Sodium chlorid	8 per cent.
Lithium phosphate	trace
Water of hydration (by difference)	3 per cent.

2. THE JOURNAL A. M. A., Feb. 7, 1914, p. 472.

"Sal Hepatica, therefore, is essentially an effervescing mixture of dried sodium sulphate (Glauber's salt) and sodium tartrate with a little dried sodium phosphate and table salt added. It is similar to the effervescent artificial Carlsbad Salt described in the National Formulary.

"In 1909 the *Druggists Circular* published the following analysis of Sal Hepatica:

Sodium phosphate	29.80 parts
Sodium sulphate (Glauber's salt)	26.27 parts
Sodium bicarbonate (baking soda)	18.00 parts
Sodium chlorid (salt)	13.05 parts
Lithium phosphate	0.04 parts
Citric and tartaric acids (to make 100)	12.84 parts

"A comparison of the recent analysis with the earlier one would seem to indicate that considerable changes have been made in the formula since the first examination. The proportions of sodium phosphate have been greatly reduced, while the sodium bicarbonate and tartaric acid have been increased and the citric acid entirely eliminated."

Sal Hepatica, then, is a simple effervescent saline laxative, essentially secret in composition and sold under claims that would be laughed at were the full formula of the product a matter of public knowledge. The following journals advertise this product:

Medical Woman's Journal
Southern California Practitioner
Therapeutic Gazette
Western Medical Times
Memphis Medical Monthly
Archives of Pediatrics
Eclectic Medical Journal
Hahnemannian Monthly
Journal of National Medical Association
International Journal of Surgery
Medical Sentinel
Indianapolis Medical Journal
Medical World
Journal-Lancet
Medical Critic and Guide
Medical Times
American Medicine
Medical Brief
Laryngoscope
Medical Record
Medical Review of Reviews
New York Medical Journal
Medical Herald
Chicago Medical Recorder
Medical Standard
Southern Medicine and Surgery
American Journal of Clinical Medicine
Medical Summary
Western Medical Review
Albany Medical Annals

Details of Analysis

Sodium Phosphate.—Phosphate was determined in a diluted solution of the mixture by precipitating with magnesia mixture, dissolving the precipitate in dilute hydrochloric acid, reprecipitating by the addition of an excess of ammonia water and a few drops of magnesia mixture, collecting the second precipitate in a weighed Gooch crucible, drying the precipitate, heating in the usual way and weighing as magnesium pyrophosphate. The filtrate from the first precipitate was made acid with nitric acid, warmed and ammonium

molybdate solution added. No yellow precipitate was given, thus demonstrating the complete precipitation of the phosphate by magnesia mixture in the presence of a tartrate. From a solution representing 2.50964 gm. of the original material, 0.0852 gm. of magnesium pyrophosphate was obtained, equivalent to 10.92 per cent. of hydrated sodium phosphate, $Na_2PHO_4+12H_2O$. Another solution representing 5.01928 gm. of original material gave 0.1720 gm. of magnesium pyrophosphate, equivalent to 11.02 per cent of hydrated sodium phosphate. A third solution representing 2.47557 gm. of original material gave 0.0852 gm. of magnesium pyrophosphate, equivalent to 11.07 per cent. of hyrated sodium phosphate. Average of three determinations: 11.00 per cent. of hydrated sodium phosphate. This is equivalent to 4.36 per cent. of anhydrous sodium phosphate, Na_2HPO_4.

Sodium Sulphate.—A weighed portion of the material (25.0964 gm.) was dissolved in water, the solution boiled in a reflux apparatus and made up to 1,000 c.c. Aliquot portions of this solution were used for various determinations. A portion of the solution was heated nearly to boiling, 2 c.c. of hydrochloric acid added followed by an excess of barium chlorid solution. The precipitate of barium sulphate was collected, heated and weighed in the usual way and the results calculated to sodium sulphate. From 25 c.c. of the solution, representing 0.62741 gm. of material, 0.2726 gm. of barium sulphate was obtained. A duplicate gave 0.2732 gm. of barium sulphate. This is equivalent to 60.04 per cent. of hydrated sodium sulphate, $Na_2SO_4+10H_2O$. A third aliquot portion of 100 c.c., representing 2.50964 gm. of material, gave 1.0930 gm. of barium sulphate, equivalent to 60.12 per cent. of hydrated sodium sulphate. Average: 60.08 per cent. of hydrated sodium sulphate. This is equivalent to 26.48 per cent. of anhydrous sodium sulphate.

Sodium Chlorid.—This was determined by the silver chlorid precipitation method in aliquot portions of the diluted solution such as was used for the sulphate determinations. From 100 c.c. of the solution, 0.5441 gm. of silver chlorid was obtained equivalent to 8.846 per cent. of sodium chlorid. A duplicate of 25 c.c. of the diluted solution, representing 0.62741 gm. of the original material, gave 0.1365 gm. of silver chlorid, equivalent to 8.877 per cent. of sodium chlorid. Average: 8.861 per cent. of sodium chlorid.

Sodium Bicarbonate.—This was determined by the Knorr method as described in the "Official and Tentative Methods of Analysis" of the A. O. A. C. ed. 1920, p. 277. From 2.2612

gm. of material, 0.2057 gm. of carbon dioxid was collected, equivalent to 19.43 per cent. A duplicate of 3.1183 gm. of material gave 0.3043 gm. of carbon dioxid, equivalent to 19.49 per cent. Average: 19.46 per cent. of carbon dioxid.

Total Sodium.—A weighed portion of the material (25.0032 gm.) was boiled with water in a reflux apparatus, the solution cooled and diluted to 1,000 c.c. An aliquot portion of this solution was neutralized with ammonia water, a slight excess of barium chlorid added to precipitate the sulphate and phosphate and the mixture allowed to stand over night. The precipitate was removed by filtration, the precipitate well washed with water, the washings added to the filtrate, an excess of diluted sulphuric acid added to the filtrate to remove excess of barium and the mixture allowed to stand over night. The precipitate was removed by filtration, the precipitate washed, the washings added to the filtrate, the filtrate evaporated in a weighed platinum dish, the residue heated to low readness, a fragment of ammonium carbonate added, the residue again heated, cooled and weighed as sodium sulphate. The sodium sulphate from 100 c.c. of this solution (equivalent to 2.50032 gm. of original material) weighed 1.8100 gm., equivalent to 23.32 per cent. of sodium. A duplicate of 25 c.c. of the solution gave 0.4494 gm. of sodium sulphate; equivalent to 23.28 per cent. of sodium. Average: 23.30 per cent. of sodium. To determine whether other metals than sodium (potassium, lithium, caesium, etc.) were present, the sulphate in the sodium sulphate was determined as barium sulphate in the usual way and the results calculated to sodium sulphate. From one-tenth of the sodium sulphate obtained from 100 c.c. of the diluted solution of the original material, 0.2987 gm. of barium sulphate was obtained. This is equivalent to 0.18187 gm. of sodium sulphate. The amount taken was 0.1800 gm. Hence, it is seen that no great proportion of foreign metals other than sodium can be present.

Lithium.—Traces of lithium were detected by the spectroscope. This was reported as lithium phosphate although there is no evidence to show that the lithium may not be present as sulphate or carbonate. The quantity present is so small that no further attention was given to it.

Tartaric Acid, Free and Combined.—(1) A portion of the material was dissolved in water and the solution boiled to expel carbon dioxid. Phenolphthalein test solution was added and sufficient sodium hydroxid test solution added to render the solution slightly pink. An excess of potassium acetate

was dissolved in the solution; an excess of glacial acetic acid and a volume of alcohol sufficient to make the alcohol content of the mixture about 40 per cent. were added. The mixture was shaken at intervals for several hours and allowed to stand over night. A white, crystalline precipitate formed.

(2) A portion of the white precipitate, obtained as described in the preceding paragraph, was washed with 50 per cent. alcohol and dissolved in hot water. The solution had an acid reaction to litmus and gave a violet color when subjected to the following test:

> If a drop of ferrous sulphate solution be added to a solution of tartaric acid or a soluble tartrate, a few drops of hydrogen peroxid solution added and the mixture finally treated with an excess of sodium hydroxid solution, a fine violet coloration is produced, which, in strong solution of a tartrate, is so deep as to appear almost black. The test is sensitive in presence of citrates or citric acid.

The above tests were considered indicative of the presence of tartaric acid in the original mixture.

A weighed portion of the material was dissolved in water in a reflux apparatus and the solution boiled to expel carbon dioxid. Phenolphthalein solution was added and the cooled solution titrated to faint alkalinity with normal sodium hydroxid. This procedure gives the value of free tartaric acid remaining after all of the sodium bicarbonate in the mixture has been consumed. Owing to the presence of phosphates in the material, which interferes to some extent with the titration, the method may be considered as an approximation. The excess acidity from 5.3266 gm. of material required 2.145 c.c. of normal sodium hydroxid, equivalent to 0.16094 gm. of free tartaric acid, or 3.214 per cent. A duplicate of 5.0558 gm. of material required 2.318 gm. of normal sodium hydroxid, equivalent to 0.17391 gm. of free tartaric acid, or 3.44 per cent. Another weight of 2.3072 gm. required 1.118 c.c. of normal sodium hydroxid, equivalent to 0.08398 gm. of tartaric acid, or 3.637 per cent. Average, 3.43 per cent. of free tartartic acid above requirements for neutralizing the sodium bicarbonate in the mixture. As previously determined, the sodium bicarbonate in the mixture calculated from the carbon dioxid content amounts to 19.46 per cent. This is equivalent to 17.38 per cent. of free tartaric acid. The sum of 17.38 per cent. of tartaric acid and 3.43 per cent. of tartaric acid is 20.81 per cent of tartartic acid. This represents the uncombined tartartic acid in the mixture at the time of analysis. In addition to this quantity of free tartaric acid

there is also a quantity of sodium tartrate which is formed from the interaction of free tartaric acid and sodium bicarbonate during the process of manufacture. Probably this decomposition takes place to some extent also during storage.

Total tartaric acid was determined by boiling a weighed quantity of the material with water in a reflux apparatus, neutralizing with sodium hydroxid in presence of phenolphthalein, evaporating the solution to dryness, igniting the residue and determining the carbon dioxid in the ash by the Knorr method. The carbonate in the ash could not be determined by direct titration with standard acid because the presence of phosphates or pyrophosphates in the ash interferes to some extent with the action of the indicators. The method for the direct titration of the ash has been employed by Vanderkleed and Turner[1] for the estimation of the total organic acids in granular effervescent mixtures but the method is inexact if the original mixture contained phosphates. The ash from 5.0723 gm. material gave 0.4464 gm. of carbon dioxid. This is equivalent to 1.542684 gm. of tartartic acid or 30.41 per cent. In a duplicate determination 24.7557 gm. of material were dissolved in water in a reflux apparatus, the solution boiled, exactly neutralized with normal sodium hydroxid and made up to 1,000 c.c. with water, The total tratrate was then determined in 250 c.c. of this solution by the method described above. The ash obtained from 250 c.c. of the solution (representing 6.188925 gm. of original material) gave 0.5641 gm. of carbon dioxid, equivalent to 31.10 per cent. of tartaric acid. Average, 30.75 per cent. of total tartaric acid.

The total tartaric acid was also estimated as follows:

> A weighed portion of the material was dissolved in water and the solution boiled to expel carbon dioxid. Phenolphthalein test solution was added and sufficient sodium hydroxid test solution added to render the solution slightly pink. An excess of potassium acetate was dissolved in the solution; an excess of glacial acetic acid and a volume of alcohol sufficient to make the alcohol content of the mixture about 40 per cent. were added. The mixture was shaken at intervals for several hours and allowed to stand over night. A white, crystalline precipitate formed. The crystalline precipitate was collected on a filter, washed with 50 per cent. alcohol, dissolved in hot water and titrated with normal sodium hydroxid, using phenolphthalein as indicator.

A weight of 7.6338 gm., after the treatment as above described, required 15.17 c.c. of normal sodium hydroxid,

1. Methods for the Analysis of Granular Effervescent Salts, A. Ph. A. Proc. **54**: 412, 1906.

equivalent to 2.30479 gm. of total tartaric acid, or 30.98 per cent. A duplicate of 10.18495 gm. of original material required 20.436 c.c. of normal sodium hydroxid, equivalent to 3.0665 gm. of total tartaric acid, or 30.11 per cent. Average, 30.55 per cent. of total tartaric acid. The average of total tartaric acid as determined by both methods is 30.65 per cent. Since the average content of free tartaric acid in Sal Hepatica is 20.81 per cent. and the total tartaric acid is 30.65 per cent., the combined tartaric acid is represented by the difference between these values, or 9.84 per cent. This is equivalent to 12.724 per cent. of sodium tartrate.

Citric Acid.—(1) A portion of the material was dissolved in water and boiled. A portion of the solution was subjected to Denige's test for citric acid. As carried out in this examination the test is as follows:

> About 1 gm. of mercuric oxid is dissolved in 25 c.c. of 35 per cent. sulphuric acid, using heat if necessary. About 1 c.c. of the reagent is added to about 5 c.c. of the suspected citric acid solution, the mixture heated to boiling and a few drops of tenth-normal potassium permanganate added. If citric acid or a citrate be present a white precipitate which consists of mercuric acetone-dicarboxylate should be produced. The test is sensitive in presence of tartrates.

As applied to Sal Hepatica the result was negative.

(2) Another portion of the aqueous solution was neutralized with normal sodium hydroxid, an excess of calcium chlorid solution added and the mixture allowed to stand for several hours. A white precipitate formed. This was removed by filtration and the filtrate boiled. On cooling and long standing small quantities of a white precipitate formed. This precipitate was collected on a filter, washed with water, suspended in very dilute sulphuric acid and boiled. The Denige test for citric acid was applied to this solution but the result was negative.

Granular effervescent salts, as obtained on prescriptions, are complex mixtures containing bicarbonates (or carbonates), organic acids and frequently sugars, in addition to the medicinal ingredient or ingredients. The acidifying agent employed is either citric acid or tartaric acid or a mixture of the two. The sugar is generally sucrose although lactose might be used. During the process of manufacture and in the storage of granular effervescent preparations, chemical reaction takes place to a greater or less extent so that the finished product varies considerably in composition from a simple mixture of the ingredients from which the preparation had been prepared. As dispensed, the prepara-

tions are in a state of unstable equilibrium ready to continue the chemical interactions whenever the conditions of moisture become suitable. Most granular effervescent mixtures are designed to contain more organic acid than is necessary to combine with the bicarbonate present, so that their aqueous solutions have an acid reaction and slightly sour taste after the effervescence has ceased.

In the analysis of granular effervescent mixtures, it is desirable to state, so far as is possible, the amounts of the various ingredients used in the manufacture of the preparations. Sometimes this is a problem of great complexity owing to the variety of the ingredients used. From the results obtained in the analysis of Sal Hepatica, it is calculated that the ingredients which had been used in the manufacture of the preparation and their proportions were essentially as published in the report of the Laboratory above.

INTRAVENOUS COMPOUND (LOFFLER)

(Abstracted, with additions, from The Journal A. M. A., Nov. 12, 1921, p. 1591)

For some time past THE JOURNAL A. M. A. has received inquiries regarding Charles Lyman Loffler, his Post-graduate Course in Intravenous Therapy and especially relative to "Intravenous Compound (Loffler)." For instance a physician writes:

"Can you tell me anything about the Physicians Drug Syndicate. . . . They are pushing the sale of Thymozene and offering One Hundred Dollars worth of stock fully paid and non-assessable, free to those sending in their order, and also a copy of Dr. Loffler's Lectures on the Blood."

And from another physician:

"What do you know of Charles Loffler, M.D., and his Intravenous Compound? A few evenings ago a man who appeared to be about 40 years old came to my office and tried to interest me in the above mentioned article; he claimed to be Dr. Charles Loffler of Chicago. With him was a young lady whom he introduced as Miss B———.

And this also:

"My attention has been called by another physician to Loffler's Intra-Venous Compound. May I trouble you to give me any information that you may have with regard to its composition and its value as a therapeutic agent?"

C. L. Loffler does business from Rooms 1101-1102, Venetian Bldg., Chicago, the location of the "Intravenous Chemical

Co.," the "Physicians Drug Syndicate" and the "Ma-Oze Chemical Co."

Charles L. Loffler's "specialty" is "Intravenous Medication." In 1912 and 1913, as the Intravenous Company of Colorado Springs, he was sending out a booklet entitled "Consumption." This described the alleged marvelous results to be obtained in the treatment of tuberculosis by the use of "Intravenous Compound"; there was also a side line, "The Loffler Internal Bath Plate." At that time the administration of "Intravenous Compound" was recommended intravenously, hypodermically, by rectum, by mouth and even by insufflation.

In addition to the Intravenous Compound (Loffler) there is, of course, certain "apparatus for the giving of the treatment" which the Intravenous Chemical Co. supplies.

The complete apparatus, including 2 ounces of Intravenous Compound (Loffler), sells for $24. What is Intravenous Compound? Apparently, nobody knows except Charles L. Loffler who asks physicians to inject—and we regret to say some are injecting—this nostrum of unknown composition into the veins of their patients. To a physician who had raised the point of secrecy Loffler wrote in part:

"I am sure that you will agree with me that it is far better to place this treatment in the hands of competent physicians, such as Dr. Witherstine, and many more whose names I will gladly send you, and to protect the honest and competent doctor who investigates and takes up the work, than to publish the formula and give to the unscrupulous a chance to try to make the product and no doubt to claim to cure disease that is beyond hope. The formula is not kept secret for profit . . . but is so kept upon the advice of a number of good men who have the interest of the doctor at heart. . . . I am willing and anxious to place the product and the results in thousands of cases before the A. M. A. on the one condition that the formula shall be kept secret for the benefit of the reputable physician."

In another letter written more recently to a physician who called attention to the secrecy of the nostrum, Loffler wrote:

"The Intravenous Compound contains approximately 58 per cent. oxygen, 12 per cent. chlorine, 16 per cent. potassium, 9 per cent. sodium and 5 per cent. boron. I have no hesitancy in giving it, and it was due to an incompetent man in this office that this was not given fully in the booklet. He made the changes without my consent and has caused me to answer many inquiries by physicians."

A seeming frankness is a trick as old as nostrum exploitation itself. Loffler's "formula" is meaningless. A quack who was putting out a mixture of 1 part baking soda and 2 parts common salt might with equal frankness say that his mar-

velous combination contained approximately 35.4 per cent. sodium, 4.8 per cent. carbon, 19 per cent. oxygen, 40.4 per cent. chlorin, and 0.4 per cent. hydrogen.

In order that the profession might know more about this product a specimen was turned over to the Chemical Laboratory for examination.

LABORATORY FINDINGS

One original 2 ounce bottle of "Intravenous Compound (Loffler) for Intravenous Use" was submitted to the Association's Chemical Laboratory for examination; according to the label the product is sold by the "Intravenous Chemical Co., Chicago." The bottle contained a white granular substance, which appeared as if the ingredients had been fused together. The product responded to tests for sodium, potassium, chlorate, borate and nitrate. As this same set of chemical radicals was found by Puckner and Hilpert (J. A. M. A., May 22, 1908, p. 1706) to be present in "Oxychlorin" and "Zyme-oid," a quantitative comparison of "Intravenous Compound (Loffler)" was made.

The analysis indicated that all three products are essentially the same:

	Oxychlorin Per Cent.	Zyme-Oid Per Cent.	Intravenous Compound Per Cent.
Potassium (K^+)	12.26	13.50	13.79
Sodium (Na^+)	8.20	9.84	9.82
Boric acid anhydride (B_2O_3)	18.63	13.42	15.20
Chlorate ($Cl\ O^-_3$)	25.52	27.53	26.44
Nitrate (NO^-_3)	21.70	24.22	23.75
Water calculated	13.29	10.42	11.72

Assuming that the chlorate in "Intravenous Compound (Loffler)" is present as potassium chlorate and the nitrate is present as sodium nitrate, the figures obtained by the analysis correspond to a mixture approximately as follows:

Potassium chlorate ($KClO_3$)	38.6 per cent.
Sodium nitrate ($NaNO_3$)	32.6 per cent.
Potassium borate ($K_2B_4O_7$)	4.9 per cent.
Sodium borate ($Na_2B_4O_7$)	4.0 per cent.
Boric acid	21.1 per cent.

From the results of the examination it is concluded that this preparation is a mixture of alkali chlorate and nitrate and boric acid probably produced by fusing together the constituents. It is practically the same mixture as Oxychlorine and Zyme-oid as analyzed nearly fourteen years ago in the A. M. A. Chemical Laboratory.

In commenting on this preparation THE JOURNAL stated:

"'Intravenous Compound (Loffler)' stands revealed as a nostrum of secret composition which physicians are asked to inject into the veins of their patients. It must be purchased in connection with some supplementary material, 'a complete set of apparatus,' sold by the same concern. Its successful administration is said to depend on following a technic detailed either in a booklet sent out by Loffler or given by Loffler in a 'Post-graduate Course' which costs physicians $50 unless they have purchased six dollars' worth of another nostrum, 'Thymozene.'

"The intravenous administration of drugs is impressive. To the patient the technic is mysterious and its psychic effect striking. Its dangers—infection, air-embolism, intravascular clotting, sudden death—are matters of record. Every conservative physician will admit that there is no excuse for the intravenous administration of even those drugs that are well known and whose effects have been carefully studied, except when distinct advantages are to be secured. As THE JOURNAL has stated before, 'little is known of the results to be expected from intravenous therapy even with simple substances.' Intravenous Compound (Loffler) has been on the market ten years; it is unmentioned in the literature of scientific medicine. The name of its exploiter while not unknown in the twilight zone of professionalism as the exploiter of a nostrum, as a 'Specialist' in 'Chronic Troubles' and 'Intravenous Therapy,' as well as in other capacities even less savory, is equally unknown to scientific medicine."

Details of Analysis

Sodium and Potassium.—(a) The borate radical was removed from 1.0916 gm. of sample by distillation with methyl alcohol. The residue was transferred with washings to a volumetric flask and made up to 100 c.c. (Solution "A"). Fifty c.c. of the dilution were pipetted into a weighed dish, 10 c.c. of diluted sulphuric acid added and the solution evaporated to dryness by aid finally of a free flame. A few drops of concentrated sulphuric acid were added, the mixture again evaporated to dryness and the residue heated to constant weight. The combined weight of sulphates was 0.3249 gm., equivalent to 0.6498 gm. for the entire sample. Twenty-five c.c. of solution "A" were acidified with hydrochloric acid and the solution treated with chlorplatinic acid in the

usual manner. The yield of potassium platinic chlorid was 0.2335 gm., equivalent to 0.3344 gm. of potassium sulphate in the sample. Calculating, the percentage of potassium equals 13.77 and that of sodium equals 10.28. (b) The borate radical was removed from 0.7660 gm. of sample by distillation with methyl alcohol. The residue was transferred with washings to a weighed dish, 15 c.c. of diluted hydrochloric acid added and the solution evaporated to dryness over a steam bath. More hydrochloric acid (1:1) was added and the mixture evaporated; this operation was repeated. The chlorids were then dried to constant weight at 120 C., care being taken to avoid loss by decrepitation. The chlorids weighed 0.3827 gm. The combined chlorids were dissolved in water and made up to 50 c.c. in a volumetric flask. Twenty-five c.c. of the solution were treated with chlorplatinic acid, and the potassium chlorplatinate reduced to platinum. The weight of platinum was 0.1316 gm. Calculating, the percentage of potassium equals 13.82 and that of sodium equals 9.35.

Boric Acid Anhydride (B_2O_3).—This was determined in the presence of glycerol according to the procedure of R. T. Thomson using methyl red as an indicator. (a) A sample weighing 3.2650 gm. required 14.19 c.c. of normal sodium hydroxid, equivalent to 15.20 per cent. of boric anhydrid (B_2O_3). (b) 3.8758 gm. required 16.84 c.c. of normal sodium hydroxid, equivalent to 15.20 per cent. of boric anhydrid (B_2O_3).

Chlorate (ClO_3).—Chlorate was determined by the short method of reduction with ferrous sulphate, dissolving the ferric base in nitric acid and weighing as silver chlorid. A weight of (a) 0.9118 gm. yielded 0.4238 gm. of silver chlorid. A weight of (b) 0.3537 gm. yielded 0.1568 gm. silver chlorid; average, 26.44 per cent. of chlorate ion.

Nitrate (NO_3).—The nitrate was determined by reduction in alkaline solution with aluminum and zinc dust, allowing the reduction to proceed over a period of hours. The ammonia was caught in standard acid. A weight of 2.7712 gm. of the specimen was dissolved in 100 c.c. of water. (a) Twenty-five c.c. contained sufficient nitrate (NO_3) so that the converted ammonia neutralized 2.7 c.c. of normal hydrochloric acid, equivalent to 24.16 per cent. of nitrate ion (NO_3). (b) Twenty-five c.c. neutralized 2.6 c.c. of normal acid, equivalent to 23.33 per cent. of nitrate ion (NO_3).

SELENI-BASCCA

(*Abstracted from The Journal A. M. A., Nov. 19, 1921, p. 1672*)

In discussing the propaganda for use of this preparation in cancer, THE JOURNAL, among other things stated:

"In the September 3 issue, attention was called to a campaign of free publicity that was being instituted by a Brooklyn concern that, apparently, had for sale an alleged remedy for cancer. The press-agent material was of two kinds—for medical journals and for newspapers. That which went to the medical journals was sent out on the stationery of the 'Medical News Bureau,' 77 Seventh Ave., Brooklyn. The 'manager' of the bureau was given as D. E. Woolley. The items sent out to medical journals stated that the 'Basic Cancer Research' had been organized to develop a treatment of cancer by the use of selenium and tellurium.

"The material received by newspapers was sent out by the 'Cosmopolitan Cancer Research Society,' 847 Union St., Brooklyn (the same address as the 'Basic Cancer Research'). The 'Secretary' of the 'Cosmopolitan Cancer Research' was D. E. Woolley!

"The name of one 'Dr. Frederick Klein' loomed large in the matter sent out by the 'Cosmopolitan Cancer Research Society.' Klein, we were told, is 'the eminent authority on urinology and the chemistry of cancer.' THE JOURNAL called attention to the fact that Frederick Klein's name was not unknown in the Propaganda files, as he was the gentleman who manufactured 'Sulfo-Selene,' a product that was widely heralded in the newspapers in 1916 as a remedy for cancer. It was also brought out that Klein, who is not a physician, claims to have evolved certain remarkable urinary diagnostic tests whereby the presence of cancer, syphilis, etc., may be determined.

"At the time of THE JOURNAL'S article the name of the particular preparation which the Basic Chemical Corporation of America was putting out was unknown. Shortly after the article appeared it was learned that the product was on the market as 'Seleni-Baseca.' A physician, himself a sufferer from carcinoma, after reading the article of September 3, sent THE JOURNAL some correspondence he had received from the Cosmopolitan Cancer Research Society regarding the alleged cure. One piece was a letter signed 'F. W. Humphrey, Acting Director; Dictated by Dr. George D. Barney,' which read in parts:"

"Our claim is a very simple one indeed, namely, that the use of a proper preparation of Selenium (Seleni-Bascca) restores the Sulphur metabolism to normal; we claim that cancer cannot exist in any form, when the Sulphur metabolism is normal, the results from the proper use of Seleni-Bascca in cases of Carcinoma are quick and lasting, the Medical Profession can hardly realize that in this modest treatment a remedy for the Dreaded Carcinoma has been discovered.

"Seleni-Bascca in it's colloidal form is quickly taken up by the blood stream, reaches the finest tissues and almost immediately resists the further growth of the disease. The research work has been going on since 1901, under the direction of Dr. Frederick Klein, in connection with Medical Men who have proved to their own satisfaction that Seleni-Bascca should be used as a treatment in every case of malignancy."

Seleni-Bascca comes in small vials containing fifty tablets. Each vial bears a label reading:

"*SELENIBASCCA.* A mixture of Colloidal Selenium in tablet form. Recommended in the internal treatment of Carcinoma and some other cases of faulty metabolism."

Some of the preparation was turned over to the A. M. A. Chemical Laboratory with the request that the tablets be examined to determine whether or not they contained, as claimed, selenium in colloidal form. The laboratory report follows:

LABORATORY REPORT

An original vial of "Seleni-Bascca" (Basic Chemical Corporation of America) was examined in the A. M. A. Chemical Laboratory to determine whether or not the substance contained colloidal selenium. The bottle contained 50 tablets weighing approximately 0.1 gm. (about 1½ gr.) each. The major portion of the tablet was soluble in hot water. Qualitative tests indicated the presence of chlorid, sulphate, small amount of nitrate, potassium, sodium, starch, talc and selenium. Tellurium was not found to be present. The ash was equivalent to 5.5 per cent.; over one half of the ash consisted of a talc-like substance. The amount of selenium present in the specimen examined was only about 1.3 per cent.

In the literature sent out by The Basic Chemical Corportion, "Dr. Frederick Klein" is mentioned as chemist. Several years ago, the Council on Pharmacy and Chemstry investjgated "Sulfo-Selene," a cancer remedy, with which the same "Dr. Klein" was connected. The alleged composition of "Sulfo-Selene," as given to the Council, was:

"Selenium	.25
"Sulphur (partially in colloidal and partially in crystalloid state)	.10
"Potassium carbonate	.10
"Nitrogen	.05
"Bile Salts	.50

"To which is added an inert base or vehicle; as sugar of milk or amylum."

It was claimed that "Sulfo-Selene" was prepared by reducing nitro-selenious acid with sulphurous acid, neutralizing with potassium bicarbonate and then adding bile salts. Assuming that the composition claimed for "Sulfo-Selene" was correct the analysis of "Seleni-Bascca" shows that the two products resemble each other. The tests, however, failed to reveal in "Seleni-Bascca" the presence of the bile salts claimed to have been present in "Sulfo-Selene."

The product is not colloidal as claimed as the selenium can be removed by ordinary filtration.

PART III

REPORTS NOT PREVIOUSLY PUBLISHED

FURTHER OBSERVATIONS ON ACRIFLAVINE AND PROFLAVINE

L. E. Warren, PhC., B. S.

Since the tentative standards for acriflavine and proflavine were proposed by the Laboratory two years ago (Rep. Chem. Lab. A. M. A. Vol. 12, 1919, p. 64) a number of additional market specimens of the two substances have been examined. Some of these products were found to conform to the tentative standards and have been admitted to New and Nonofficial Remedies. Others did not conform to the standards proposed. Specimens were examined which had been sub-

TABLE 1

Brand	Loss on Drying	Water Insoluble	Ash	Chlorin
Acriflavine Abbott	6.34	0.05	0.17	22.07
Acriflavine Heyl (1920 purchase)	5.01	0.40	1.46	.....
Acriflavine Heyl I (1920 submission)	5.11	0.10	0.59	.....
Acriflavine Heyl II (1920 submission)	4.82	negligible	0.70	.....
Acriflavine Heyl III	6.17	0.60	0.47	25.61
Acriflavine Van Dyk I (United Synthetic Corp.)	20.52 19.09	1.46	1.11	.....
Acriflavine Van Dyk II (United Synthetic Corp.)	10.93	0.23	0.36	22.26
Acriflavine Boots (Old sample)	....	....	....	22.46
N. N. R. standards	Not over 10	1	1	12.772* per cent.
Formula 2 atoms Cl	....	....	....	22.73

* Requirement of formula.

mitted by the Abbott Laboratories, by the Heyl Laboratories, and by the United Synthetic Chemical Corporation (Van Dyk). The findings for the several specimens are tabulated herewith, the N. N. R. standards being given for comparison.

A question arose concerning the amount of hydrochloric acid in acriflavine. The statements in the literature indicate that the product contains but one molecular equivalent of

acid. The formula given in N. N. R. 1921 was based on the formula as given by May (Chemistry of Synthetic Drugs ed. 2, p. 173). This compound according to the May formula should contain 12.77 per cent. of chlorin. The attention of the Laboratory was called to the assertion that acriflavine con-

TABLE II

Brand	Loss on Drying	Water Insoluble	Ash	Sulphuric Acid H_2SO_4
Proflavine Abbott	7.32	0.38	0.33	31.85
Proflavine Heyl (1920)	4.24	0.73	0.14	.....
Proflavine Heyl (1920)	8.42	1.97	0.85	28.36
Proflavine Heyl (1920)	....	0.91	0.52	32.51
Proflavine Heyl (1921)	0.12	0.84	0.44	.....
Proflavine Van Dyk I	2.19	6.87	0.48	29.05
Proflavine Van Dyk	5.67	2.10	0.34	.....
N. N. R. standards	Not over 10 per cent.	Not over 1 per cent.	Not over 1 per cent.	Theory 30.19

tained two atoms of chlorin instead of one. In order to determine whether the claims were true, the chlorin in several specimens of acriflavine was determined by precipitating with silver nitrate and weighing as silver chlorid. The findings were varied, but they indicate that the product contains about two atoms of chlorin rather than one. The findings are tabulated in the fifth column of Table I.

POTASSIUM MERCURIC IODID

Paul Nicholas Leech., Ph. D.

In recent months, the use of potassium mercuric iodid as a germicide has increased. For a number of years, potassium mercuric iodid (*Potassii Hydrargyri-Iodidum*) has been described in the respective editions of *New and Nonofficial Remedies;* the description, which is given herewith, was rather meager in tests of identity and purity:

> "When mercuric iodid is added to an excess of potassium iodid solution, a colorless liquid is obtained containing the mercuric iodid as a complex salt, approximately K_2HgI_4 (or $2KI + HgI_2$). Under suitable conditions (Naylor and Chappel: *Pharm. Jour.*, March 7, 1908, p. 315), the salt having the composition $K_2HgI_4 + 3H_2O$ (or $2KI + HgI_2 + 3H_2O$) may be obtained in yellow needle-shaped crystals.
>
> "Potassium mercuric iodid is deliquescent."

Therefore, it was thought advisable at this time to investigate representative specimens of the product, to the end that the description in New and Nonofficial Remedies might be

elaborated, especially since another brand had been submitted to the Council on Pharmacy and Chemistry for inclusion in New and Nonofficial Remedies.

Solubility.—One mol Mercuric Iodid is soluble *theoretically* in a solution containg 2 mols potassium iodid, forming the complex salt $HgI_2+2KI \rightarrow K_2HgI_4$. However, potassium mercuric iodid undoubtedly dissociates as

$$HgI_2+2KI \rightleftarrows K_2HgI_4 \rightleftarrows 2K^{+}+HgI_4^{--}$$
$$\downarrow\uparrow$$
$$Hg^{++}+4\,I^{-}$$

In the presence of considerable water there would be a tendency for some mercuric iodid to be formed, which, because of its insolubility, would precipitate. This is actually what happens. Potassium mercuric iodid dissolves in a very small amount of water, but when diluted, sufficient dissociation occurs so that the precipitated mercuric iodid is quite perceptible. So, in order to have stable solutions containing potassium mercuric iodid, potassium iodid is necessary.

Reactions.—The elemental components of potassium mercuric iodid are identified easily. One c.c. of a 20 per cent. solution, after addition of ferric chlorid solution, imparts the characteristic iodin coloration to a chloroform layer. The addition of formaldehyde solution to potassium mercuric iodid solution, previously made alkaline with sodium hydroxid, causes a precipitation of black metallic mercury. When some of the dry salt is ignited in a porcelain dish, the residue gives the usual qualitative tests for potassium.

QUANTITATIVE DETERMINATIONS

Moisture.—The moisture content of potassium mercuric iodid was determined by loss in weight after drying in an oven at 120 C. for four hours.

Potassium.—About 0.5 gm. accurately weighed of potassium mercuric iodid was placed in a tared platinum dish and concentrated sulphuric acid added carefully. The mixture was heated gently until there were no fumes of sulphur trioxide or iodin. The dish was then subjected to a free flame until dull red; it was then cooled, a few drops of sulphuric acid added, and the acid evaporated. The dish was then heated until all the sulphate had been converted to normal sulphate. The mercury, of course, was volatilized during the treatment, so that the residue was pure potassium sulphate and weighed as such.

Mercury.—The electrolytic method of determining mercury is preferable to the older methods because of its greater ease

and accuracy; it is the determination described in the U. S. Pharmacopeia IX. The pharmacopeia directs that mercury compounds of the type of mercuric iodid be dissolved in sodium sulphid solution; that the current throughout shall be from 2 to 3 amperes and 7 to 10 volts; also that the mercury be dried by washing with alcohol, then ether and removing most of the remaining ether with filter paper; final drying is in a desiccator over sulphuric acid.

In the work reported in this paper, the following departures from the foregoing were made:

1. Sodium hydroxid was used in place of sodium sulphid. Sodium sulphid often leaves deposited particles on the mercury, the solution is not clear and a pure preparation is not always obtainable. Sodium hydroxid meets all these objections. Its alkalinity is also suitable to convert the iodin formed at the cathode into an oxygen salt.

2. A low amperage was employed in the forepart of the electrolysis, gradually increasing until that recommended in the pharmacopeia was attained. Under this procedure, the iodin was not freed at the pole so fast that it "sprayed up" onto the glass cover. The electrolysis was carried out for forty minutes.

3. The mercury was washed, as in the pharmacopeia with alcohol; however, ether was not used. Ether, unless quite recently distilled, seems to contain impurities (peroxides?) which react with the mercury in such a manner that a film is formed; this film may also stick to the sides of the vessel and to filter paper. After washing the mercury with alcohol, omitting use of any ether, and removing as much liquid as possible by dipping with filter paper, the vessel was placed in a desiccator over potassium hydroxid sticks and a beaker of dry mercury. The mercury already present is presumed to have saturated the air in the desiccator with mercury vapors. Potassium hydroxid absorbs less mercury, it is stated, than does sulphuric acid.

It was found that just as accurate results could be obtained in determining mercury in potassium mercuric iodid by substituting a 120 c.c. platinum dish for a cathode cup. The mercury adhered well and was easily washed. Practically no sodium amalgam was formed as is the case in the cathode cup, shortening the time of treatment with acetic acid. The pharmacopeial method with modification was recommended in the assay as submitted to the Council.

Iodin.—The method found most adaptable was that of L. W. Andrews (*J. Am. Chem. Soc.* XXV, 756); it has also

been recommended by A. J. Jones (Mercuric Potassium Iodid Tablets; *Chemist and Druggist*, April 17, 1920, p. 69). It is based on the influence of iodate in a strong acid solution.

$$2HI + HIO_3 + 3HCl \rightleftarrows 3H_2O + 3ICl.$$

It will be noted in this titration that the decinormal potassium iodate solution contains 10.701 grams per liter of the salt.

Results.—Two brands of potassium mercuric iodid were analyzed:

"Mercury and Potassium Iodid-Merck."

"Mercury and Potassium Iodid-P. W. R."

The results were:

	Merck	P. W. R.
Moisture	2.88	3.40
Potassium (K^+)	9.91	9.52
Mercury (Hg^{++})	24.61	24.71
Iodin (I^-)	61.8	61.7

Several years ago the A. M. A. Laboratory analyzed the mercury content of "Soloid Mercuric Potassium Iodide" tablets (Annual Reports A. M. A. Chemical Laboratory Volume 1, p. 72). These tablets according to New and Nonofficial Remedies are claimed to contain potassium mercuric iodid 0.113 gm. (1.75 grains), an excess of potassium iodid and a trace of coloring matter. It was found at that time that each tablet contained 0.118 gm. of potassium mercuric iodid and 0.101 gm. excess of potassium iodid.

Description by Council.—After the Laboratory had reported its findings and made its recommendation, The Council adopted the following description for inclusion in New and Nonofficial Remedies:

POTASSIUM MERCURIC IODID.—Potassii Hydrargyri Iodidum.—A complex salt, K_2HgI_4, formed by the interaction of one molecule of mercuric iodid with two molecules of potassium iodid and containing about 25.5 per cent. of mercury.

Actions and Uses.—Potassium mercuric iodid is used for the same purpose as mercuric iodid, over which it has some advantages because of its solubility. As a germicide it is effective as it does not coagulate albumin; however, there seems to be no work to show how much the activity is decreased when an excess of potassium iodid is present. In comparison with mercuric chlorid it is claimed to have a greater safety factor: Weight for weight, potassium mercuric iodid is about one half as toxic as mercuric chlorid according to animal experiments; in proportion to the mercury

content, however, potassium mercuric iodid and mercuric chlorid possess about the same toxicity.

Externally, potassium mercuric iodid is used for skin disinfection, irrigations, disinfection of instruments, and of excreta and discharges.

Dosage.—As a germicide it is used in concentrations of 1 : 100 to 1 : 10,000. For irrigation of wounds, it is desirable to render the solution isotonic by addition of 0.9 per cent. sodium chlorid. Solutions of potassium mercuric iodid may be prepared:

(1) By dissolving 1 part by weight of mercuric iodid and 1 part by weight of potassium iodid in a small amount of water and then diluting to proper strength; such a solution will contain about 20 per cent. excess of potassium iodid, sufficient to prevent precipitation of mercuric iodid from dilute solutions of the complex salt. (1 gm. mercuric iodid is equivalent to 1.7 potassium mercuric iodid.)

(2) By dissolving potassium mercuric iodid in water containing potassium iodid. Solutions made from potassium mercuric iodid alone have a tendency to decompose with precipitation of mercuric iodid; hence it is necessary to have present an excess of potassium iodid equivalent to about 20 per cent. by weight of the amount of potassium mercuric iodid used.

Potassium mercuric iodid occurs as yellow crystals, deliquescent in air. It is soluble in alcohol and in potassium iodid solution. It yields a clear solution with one part of water. When the solution is diluted with much water, mercuric iodid precipitates slowly; but if one fifth of its weight of potassium iodid is previously added to the salt or its concentrated solution, no mercuric iodid separates on its dilution. Its aqueous solution is slightly alkaline to litmus. When the salt is heated in a test tube to the point of fusion, it becomes red, but on cooling again assumes a yellow color; at higher temperatures there is volatilization of mercuric iodid.

Treat about 0.2 gm. of potassium mercuric iodid with 1 c.c. of water, add 1 c.c. of chloroform and 0.5 c.c. of ferric chlorid solution; the chloroform shows the characteristic color of iodin. Treat about 0.1 gm. of the salt with 2 c.c. of sodium hydroxid solution, and add a few drops of formaldehyd solution; a black precipitate of metallic mercury is produced.

Potassium mercuric iodid loses not more than 4 per cent. of its weight when dried in a hot air oven at 120 C. for four hours.

Transfer about 1.5 gm. of potassium mercuric iodid, accurately weighed, to a 100 c.c. volumetric flask and dissolve in 1.5 c.c. of water, then dilute to 100 c.c. Pipet immediately 10 c.c. of the solution into a glass stoppered 250 c.c. bottle, add 35 c.c. of hydrochloric acid and 5 c.c. of chloroform. Titrate the solution with tenth-normal potassium iodate (10.701 gm. in 1,000 c.c.), stoppering the bottle and shaking the contents well after each addition. The reaction is carried on until the iodin which was first liberated disappears, and the chloroform shows no pink color. The iodin content, calculated to the dry salt, is not less than 63.4 per cent. nor more than 65.5 per cent.

Dissolve about 2.5 gm. of potassium mercuric iodid, accurately weighed, in about 10 c.c. of water, and add sufficient potassium iodid solution to prevent precipitation of mercuric iodid. Introduce the solution and washings into a cathode cup, previously weighed with its metallic mercury, and add 10 c.c. of sodium hydroxid solution, 20 per cent. Pass through the solution an electric current, gradually increasing the current so that at the end of eight minutes it will be 2 to 3 amperes and 7 to 10 volts, stirring the solution by rotating the anode about 500 revolutions per minute. After forty minutes, wash with distilled water, with the aid of a siphon and without interrupting the current until the current drops to zero. Remove the cathode cup and allow it to stand with 20 c.c. of acetic acid solution, 3 per cent., until bubbles cease to be evolved. Wash the mercury with water, and then alcohol; remove most of the excess alcohol by filter paper, then dry in a desiccator over potassium hydroxid sticks and a beaker of mercury. The increase in the weight in the cathode cup represents the amount of mercury present in the quantity of the salt taken. The mercury content of potassium mercuric iodid, calculated to the dry salt, is not less than 25.0 per cent., nor more than 26.0 per cent.

Details of Analysis

MERCURY AND POTASSIUM IODID P.W.R.

Moisture.—The loss in weight of a sample weighing 2.5588 gm. was 0.0870 gm., equivalent to 3.40 per cent.

Potassium.—(a) A sample weighing 0.4130 gm. yielded 0.0876 gm. potassium sulphate, equivalent to 9.52 per cent.; (b) 0.3511 gm. yielded 0.0744 gm. potassium sulphate equivalent to 9.51 per cent. potassium (K^+).

Mercury.—(a) A sample weighing 1.5969 gm. yielded 0.3946 gm. of mercury, equivalent to 24.71 per cent. mercury (Hg^{++}). (b) 1.6179 gm. yielded 0.3997 gm. mercury, equivalent to 24.70 per cent. mercury. Calcuated to the dry salt, this is equivalent to 25.56 per cent.

Iodin (Iodid I^-).—A sample weighing 1.4681 gm. was dissolved in a very small amount of water then diluted to 100 c.c. and two 10 c.c. aliquot portions quickly pipetted into two glass stoppered bottles. (a) 10 c.c. required 7.25 c.c. of tenth normal potassium iodate, equivalent to 61.7 per cent. iodin (as iodid I^-). (b) Same as *"a."* Calculated to the dry salt, this is equivalent to 63.8 per cent.

MERCURY AND POTASSIUM IODID-MERCK

Moisture.—The loss in weight of a sample weighing 4.7402 gm. was 0.1368 gm. equivalent to 2.88 per cent.

Potassium.—(a) A sample weighing 0.5028 gm. yielded 0.1104 gm. potassium sulphate, equivalent of 9.86 per cent. potassium (K^+); (b) 0.3319 gm. yielded 0.0737 gm. potassium sulphate, equivalent to 9.96 per cent. potassium (K^+).

Mercury.—(a) A sample weighing 2.4685 gm. yielded 0.6061 gm. of mercury, equivalent to 24.55 per cent. mercury

(Hg^{++}); (b) 1.6495 gm. yielded 0.4068 gm. mercury, equivalent to 24.66 per cent. mercury. Calculated to dry salt, the average 24.61 is equivalent to 25.33 per cent. mercury.

Iodin (*Iodid* I^-).—A sample weighing 0.7081 gm. was dissolved in a very small amount of water then diluted to 50 c.c. and two 10 c.c. aliquot portions quickly pipetted into glass stoppered bottles. (a) 10 c.c. required 6.9 c.c. tenth normal potassium iodid, equivalent to 61.8 per cent. iodin (as iodid I^-). (b) Same as *"a"* Calculated to the dry salt, this is equivalent to 63.6 per cent.

SOME NOTES ON METHYL ATROPIN BROMID

L. E. Warren, Ph. C., B. S.

Methyl atropin has been known for many years. Its preparation was undertaken in the hope that an atropin derivative might be obtained which would have the mydriatic properties of atropin but which would be less toxic. It was prepared under German patents.[1] This methyl derivative was found to possess mydriatic properties. Its action was said to be more prompt and more fleeting than that of atropin. Its nitrate was introduced into medicine under the protected name, "eumydrin." Another salt, the bromid, was also placed on the market by a German firm. In England atropin methyl bromid has been sold under the name of *mydriasine*. It has been used internally for conditions similar to those for which atropin is employed; also subcutaneously in croupous pneumonia, pleurisy and appendicitis; in conjunction with sodium bicarbonate in dyspepsia; and in epilepsy together with bromids. During the war, supplies of eumydrin became unobtainable. An American manufacturer (The Werner Drug and Chemical Company) undertook the preparation of the substance in this country in the form of the bromid.

A specimen of methyl atropin bromid of American make was obtained from the manufacturer and examined. The substance was a white, crystalline, somewhat lumpy powder. It was neither deliquescent nor effloresecent. It did not lose weight when dried over sulphuric acid. It was found to be soluble in water and alcohol but only slightly soluble in ether or chloroform. Its aqueous solution was clear, colorless and neutral to litmus paper. The aqueous solution gave precipitates with many of the alkaloidal reagents, but was

1. D. R. P. 137622; 138443.

TABLE 1.—REACTIONS OF SOME OF THE MYDRIATIC ALKALOIDS

Reagent	Methyl Atropin Bromid	Eucatropine	Atropin Sulphate	Homatropin Hydrobromid
Picric acid	No precipitate	Yellow (amorphous)	Lemon yellow (crystalline)	Lemon yellow (crystalline)
Gold chlorid	Orange red, dissolves in hot water without melting	Yellow melts in hot water	Lemon yellow melts in hot water	Yellow, dissolves in hot water without melting
Palladous chlorid	Brown	No precipitate	No precipitate	No precipitate
Platinic chlorid plus hydrochloric acid	No precipitate	No precipitate	No precipitate	No precipitate
Mercuric chlorid	White (curdy)	No precipitate	No precipitate	White
Mercuric potassium iodid	White	White	White	Yellowish white
Iodin	Brown	Brown	Brown	Brown
Bromin	Yellow (crystalline on standing)	No precipitate	No precipitate	No precipitate
Phosphotungstic acid	White (flocculent)	White (flocculent)	White (flocculent)	White (flocculent)
Tannic acid	No precipitate	No precipitate	White	No precipitate
Vitali's test	Violet	Not violet	Violet	Not violet
Alcoholic mercuric chlorid test	No reaction	Brick-red precipitate	Brick-red precipitate	Brick-red precipitate

TABLE II

	M. P. of Free Base	M. P. of Hydrobromid	M. P. of Picrate	M. P. of Aurochlorid
Methyl atropin bromid	.....	222–223	Not precipitated	193–194
Atropin	112–113 115.5 114–116	162	175–176 175 174–175	135–137* 136–139 136
Hyoscyamin	108.5 108 106–108	151.8 152	161–165 161–163 161–164	160† 162–165 160–162 162
l.—Scopolamin (Hyoscin)	59	193–194 179.7	187–188 190–191	198–199 197
Homatropin	98–99 95–96 93.5–98.5	213.8 212 210–212	180–181 181 185	142–145†
Eucatropine (euphthalmin)	108–113 111–112	.....	153–157 (indefinite)	158–159* 162

* Melts in boiling water.
† Does not melt in boiling water.

not precipitated by platinic chlorid solution or by picric acid solution. Its aqueous solution gave a precipitate with palladous chlorid test solution, thus differing from the other mydriatic substances tested, the salts of which gave no precipitates. The aqueous solution gave a white, curdy precipitate with mercuric chlorid test solution. Eucatropin and atropin sulphate gave no precipitates. Homatropin hydrobromid gave a white precipitate but it was not curdy so that the last named property may be used to distinguish methyl atropin bromid from homatropin salts. It gave the Vitali test like atropin.

A comparison of some of the reactions of methyl atropin bromid and the salts of other mydriatic alkaloids was given in Volume 13 of the Reports of the A. M. A. Chemical Laboratory, 1920, pp. 64 and 66. For ease of comparison, they are reproduced, with some modifications and additions, on the previous page.

Based partly upon the information in the literature and partly upon the results of the examination of the commercial specimen of methyl atropin bromid, a tentative description of the product was prepared. This is given herewith.

Atropin methyl bromid occurs in white, crystalline masses or as a white powder; odorless; permanent in the air.

Atropin methyl bromid is very soluble in water; soluble in alcohol; slightly soluble in ether and chloroform.

Atropin methyl bromid melts at 222-223 C.

An aqueous solution of atropin methyl bromid (1: 100) is neutral to litmus.

An aqueous solution of atropin methyl bromid (1: 100) gives a yellowish-white precipitate with silver nitrate test solution which is insoluble in nitric acid. It gives precipitates with mercuric potassium iodid test solution, iodin test solution, gold chlorid test solution and many other reagents for the alkaloids, but it is not precipitated by platinic chlorid test solution or by picric acid solution.

The aqueous solution of atropin methyl bromid (1: 100) gives a brown precipitate with palladous chlorid test solution and a white, curdy precipitate with mercuric chlorid test solution (*distinction from atropin salts and homatropin salts*).

Add a few drops of nitric acid to a fragment of atropin methyl bromid, evaporate the mixture to dryness on a water bath, cool the residue and add a few drops of alcoholic potassium hydroxid together with a fragment of potassium hydroxid. A violet color results (*distinction from homatropin salts*).

Incinerate about 1 gm. of atropin methyl bromid, accurately weighed. The ash does not exceed 0.1 per cent. of the weight taken.

DOES KALNITE CONTAIN POTASSIUM ALUMINUM NITRATE?

Under the trademarked name "Kalnite" Sharp and Dohme presented to the Council on Pharmacy and Chemistry a

preparation claimed to be composed of potassium nitrate 90 parts and a new, double salt of potassium nitrate and aluminum nitrate. The product was recommended to be used in a poultice (39 grains of the salt to 3½ ounces of rolled oats) for the treatment of bone infections.

The Council asked the Laboratory to investigate the composition of Kalnite—Sharp and Dohme; the following is the report of the laboratory:

An original one-pound ("hospital") package of "Kalnite" was submitted to the Chemical Laboratory for examination.

The label on the package bore the statement: "Kalnite is the product obtained by crystallizing together synthetic aluminum potassium nitrate with an excess of potassium nitrate and represents the proper proportions to conform to the standards established by the LaPorte Clinic for the treatment of pyogenic infections. . . . The content of this package has been certified by the LaPorte Clinic, Chicago." The method of preparation, as given by the manufacturer, Sharp and Dohme, in the presentation of the product to the Council, is as follows:

> "Mix aluminum nitrate crystallized with potassium nitrate in the proportion of their molecular weight based on one molecule of aluminum nitrate to three molecules potassium nitrate in a dish on a water bath and add sufficient concentrated nitric acid to dissolve the mixture. For 213 parts of aluminum nitrate and 303 parts potassium nitrate by weight this will require about 250 parts of the acid by weight. Allow the mixture to cool when the double salt $Al(NO_3)_3 3KNO_3$ and 10 H_2O will crystallize out. The amount of water of crystallization will vary according to the conditions of the atmosphere and according to the amount of water in the nitric acid.
>
> "Furthermore, the double salt will not always be constant in composition, but according to atmospheric and other uncontrollable conditions the product may at times be made up of the three double salts — $Al(NO_3)_3.3KNO_3$; $Al(NO_3)_3.2KNO_3$; $Al(NO_3)_3.KNO_3$, and we have not been able to control the proportion of these several double nitrates or nitrate salts. The crystals are separated from the mother liquors by filtration and centrifugation and they are dried and deprived of excess free acid by placing them in vacuum over unslaked lime.
>
> "Add 10 parts aluminum potassium nitrate and 90 parts potassium nitrate to concentrated nitric acid 200 parts and heat on water bath until dissolved. Then cool and when crystallization is complete drain off crystals with suction filter and later with centrifugal and dry in vacuum over unslaked lime."

"Kalnite" is a white powder, very slightly tinted yellow, which on physical examination was not distinguishable from potassium nitrate, U. S. P. Qualitative tests demonstrated the presence of potassium, a small amount of aluminum, and nitrate; chlorid, sulphate, borates, phosphates and metals other than aluminum and the alkali metals were not found.

Quantitative estimations yielded the following:

Aluminum (Al^{+++})	00.30 per cent.
Potassium (K^{+})	36.62 per cent.
Sodium (Na^{+})	0.63 per cent.
Nitrate (NO_3^{-})	59.76 per cent.
Water	2.85 per cent.

The above is equivalent to 2.35 per cent. of aluminum nitrate (which may be calculated to 5.71 per cent. $Al(NO_3)_3.3KNO_3$) and 94.7 per cent. of potassium nitrate. No free acid was present in the specimen as it was neutral to methyl orange, although acid in reaction to methyl red and phenolphthalein.

On four successive fractional crystallizations, the product gave no evidence of crystals any different from those of potassium nitrate. The manufacturers state that 10 per cent. of aluminum potassium nitrate not constant in composition (the ten molecules of water of crystallization are probably removed totally or in part when dried in vaccum over unslaked lime) is used; however, if all the aluminum existed as $Al(NO_3)_3.2KNO_3$ and not also as other double salts $Al(NO_3)_3.2KNO_3$ and $Al(NO_3)_3.KNO_3$, Kalnite still contains 57 per cent. of the amount claimed.

From a chemical standpoint, there would seem to be no advantage in preparing a double salt of aluminum nitrate and potassium nitrate, because when used in solution a double salt acts the same as a mixture containing aluminum nitrate and potassium nitrate in the same proportion; furthermore, the manufacturers have not given evidence of the existence of this double salt. Summed up, Kalnite may be considered to be essentially potassium nitrate (saltpetre) admixed with a relatively small amount (2.35 per cent.) of aluminum nitrate.

The foregoing report was sent by the Council to Sharp and Dohme for consideration and reply. No reply was received, however, and the firm is not marketing the preparation at the present time.

The Laboratory's findings are now published as a matter of record because the manufacture of "Kalnite" has been taken up by another firm (by a somewhat different process and without claim that it contains a double salt of potassium nitrate and aluminum nitrate) and because of inquiries which have been received (Jour. A. M. A. April 30, 1921, p. 1265).

Details of Analysis

Aluminum.—The sample was dissolved in 200 c.c. water and the few particles of dust filtered out. The filtrate was heated to boiling, 50 c.c. of filtered ammonium chlorid solution were added and also sufficient dilute ammonia water so that the

odor of ammonia was faintly persistent. The precipitate of aluminum hydroxid was allowed to settle, the supernatant liquid filtered off, and finally the precipitate was transferred to the filter and washed well. The paper was burned carefully and the precipitate ignited and weight as aluminium oxid. (a) A weight of 6.5670 gm. of the specimen yielded 0.0372 gm. of aluminum oxid, equivalent to 0.30 per cent. of aluminum. (b) 11.5076 gm. of the specimen yielded 0.0683 gm. of aluminium oxid, equivalent to 0.31 per cent. of aluminum.

Potassium and Sodium.—Exactly 5 gm. of the specimen were dissolved in 500 c.c. water, aliquot portions of this solution being used both in the potassium-sodium and the nitrate determinations. (a) Twenty-five c.c. of the solution (equivalent to 0.25 gm. of material) were treated with a few drops of diluted ammonia water, the solution filtered, and the filtrate acidified with hydrochloric acid and evaporated to dryness. The residue was treated with concentrated hydrochloric acid, evaporated to dryness and this procedure repeated. The residue was dissolved in water and transferred to a platinum dish which was heated carefully until all ammonium salts were volatilized. After weighing, the residue was dissolved in water and treated in the usual manner with chlorplatinic acid. The weight of combined chlorids was 0.1773 gm. and of potassium chlorplatinate was 0.5678 gm., equivalent to 36.58 per cent. of potassium and 0.63 per cent. of sodium. (b) Twenty-five c.c. of the solution were treated as above except sulphuric acid was employed instead of hydrochloric acid, and the residue in the platinum dish weighed as alkali sulphate. The residue was dissolved in water, treated with chlorplatinic acid according to the method described in Annual Reports of the Chemical Laboratory 1919, Vol. 8, p. 54, the final product being platinum reduced from the potassium chlorplatinate. The weight of the combined sulphates was 0.2091 gm. and of platinum was 0.2290 gm. equivalent to 36.66 per cent. of potassium and 0.64 per cent. of sodium.

Nitrate.—The official "Zinc-Iron Method" (Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, 1920, p. 10, paragraph 34) was used, except that a few drops of caprylic alcohol were added also. The ammonia was distilled into 50 c.c. of tenth normal hydrochloric acid, and the excess acid titrated with ten normal sodium hydroxid. (a) Twenty-five c.c. of the solution described under "Potassium and Sodium" (equivalent to

0.2500 gm. of the specimen) yielded ammonia sufficient to neutralize 26.0 c.c. of tenth-normal hydrochloric acid, equivalent to 59.76 per cent. of nitrate radicle (NO_3). (b) Was an exact duplicate of *a*.

Moisture.—The weighed sample was heated to constant weight in an oven maintained at 120 C. The loss in weight of 2.6960 gm. of the sample was 0.0769 gm., equivalent to 2.85 per cent. of water.

BENZYL SUCCINATE

Benzyl succinate has been suggested as a substitute for benzyl benzoate in the treatment of spasm of the unstriped muscle. Its claimed advantages are that it is a solid, thus permitting its ready preparation in tablet form, that it is practically tasteless and odorless and that it contains a greater proportion of "benzyl" radical than some other benzyl derivatives used in medicine, such as benzyl benzoate.

Several brands of benzyl succinate were submitted to the Council on Pharmacy and Chemistry for inclusion in New and Nonofficial Remedies. These were examined in the Chemical Laboratory. The brands examined were Benzyl Succinate-Stearns (Esterol), Benzyl Succinate-Seydel, and Benzyl Succinate-Hynson, Westcott and Dunning.

Each product was a white, crystalline powder but having a very faint yellowish tinge; odorless; almost tasteless. A portion of each (1 gm.) was shaken with water (100 c.c.) and the filtrate tested for sulphates, chlorids, salicylates and reaction toward litums. The reaction of the filtrate was neutral or very faintly acid. This excluded the presence of succinic acid in any appreciable amounts. The tests for the other impurities named were negative. None of the specimens lost any appreciable amount of weight on drying over sulphuric acid. The ash was negligible. A solution of 1 gm. in 25 c.c. of alcohol was clear and very nearly colorless.

The melting points of the several specimens were as follows: Stearns, 44.5 to 45 C., Seydel 46.5 to 47 C., H. W. and D., 46.2 C. The saponification value was determined in two of the specimens and from this the percentage of benzyl succinate was calculated. The method used is as follows:

> Boil about 1 gm. of benzyl succinate, accurately weighed, for 1 hour in a reflux apparatus with 20 c.c. of half-normal alcoholic sodium hydroxid, cool the solution, add a few drops of phenolphthalein test solution, and titrate with half-normal hydrochloric acid until the disappearance of the pink color

Stearns brand: a weight of 0.9913 gm. required 13.266 c.c. of half-normal alcoholic sodium hydroxid, equivalent to 99.74 per cent. of absolute benzyl succinate.

Seydel brand: A weight of 0.9771 gm. required 13.346 gm. of half-normal alcoholic sodium hydroxid, equivalent to 99.46 per cent. of absolute benzyl succinate. A duplicate weight of 1.0847 gm. required 14.474 c.c. of half-normal sodium hydroxid, equivalent to 99.46 per cent. of benzyl succinate.

Based partly upon information submitted by the manufacturers and partly upon the results obtained in the examination, the following tentative description for benzyl succinate was prepared:

BENZYL SUCCINATE. — Benzylis Succinas. — Dibenzyl Succinate. — $C_6H_5CH_2.OOC.CH_2.CH_2.COO.CH_2C_6H_5$. — The dibenzyl ester of succinic acid. It contains not less than 99 per cent. of benzyl succinate.

Benzyl succinate is a white, or faintly yellowish-white, crystalline powder; odorless; almost tasteless; permanent in the air.

Benzyl succinate is almost insoluble in water, soluble in alcohol, ether and chloroform; also soluble in the fixed and volatile oils.

Benzyl succinate melts at 45 C.

Boil about 2 gm. of benzyl succinate with 30 c.c. of half-normal alcoholic sodium hydroxid in a reflux apparatus for 1 hour. Cool, filter, wash the precipitate with alcohol, dissolve the precipitate in the minimum quantity of warm water, and acidify with concentrated hydrochloric acid. Recrystallize the residue once from a few c.c. of hot water. The crystals of succinic acid melt at 182 C. To the alcoholic filtrate from the sodium succinate add 25 c.c. of water and boil until the alcohol is removed. Shake the alkaline solution twice each with 10 c.c. of ether and evaporate the solvent. The residue has the odor of benzyl alcohol.

Add about 1 c.c. of diluted sulphuric acid to 10 c.c. of tenth-normol potassium permanganate, add 0.1 gm. of benzyl succinate and warm the mixture. The odor of benzaldehyde becomes perceptible.

The solution of benzyl succinate in alcohol (1: 25) should be clear and colorless.

Shake 1 gm. of finely powdered benzyl succinate with 100 c.c. of water and filter. The filtrate should not be more than faintly acid to litmus paper (*succinic acid*) and separate portions should not yield precipitates with barium chlorid test solution (*sulphate*), silver nitrate test solution (*chlorid*) or be colored violet by ferric chlorid test solution (*salicylate*).

Incinerate about 1 gm. of benzyl succinate, accurately weighed. Not more than 0.1 per cent. of ash remains.

Boil about 1 gm. of benzyl succinate, accurately weighed, for 1 hour in a reflux apparatus with 20 c.c. of half-normal alcoholic sodium hydroxid, cool the solution, add a few drops of phenolphthalein test solution, and titrate with half-normal hydrochloric acid until the disappearance of the pink color. The amount of half-normal alcoholic sodium hydroxid consumed corresponds to not less than 99 per cent. of benzyl succinate.

AMYLZYME

Amylzyme is a proprietary pancreatic extract which is stated to convert from 110 to 130 times its weight of dry

starch to the colorless end point in 10 minutes if tested by the method adopted by the Council on Pharmacy and Chemistry and to be from 3 to 4 times as active as the pancreatin described in the U. S. P. if tested by the U. S. P. IX method. It is manufactured by the G. W. Carnrick Company.

Having been submitted to the Council for inclusion in New and Nonofficial Remedies, it was deemed best to check the claims for the digestive power of amylzyme according to the Johnson method,[1] which had previously been adopted by the Council for another proprietary pancreatic extract.

The assay method, as carried out on amylzyme, is as follows:

Agitate 100 gm. of potato starch with 100 c.c. of water and allow the starch to settle. Pour off the supernatant liquid, discard it and repeat the washing process four more times. Dry the starch on glass plates in the air until it can be passed through a No. 60 sieve. Dry the powder at 80 C. until sensibly free from moisture. Preserve for use in a well stoppered container.

Preliminary to the digestive tests, dry about 1 gm. of the starch, accurately weighed, to constant weight at 100 C. From the results obtained, calculate the moisture in the starch to be used for testing. In the digestive tests use such a quantity of the undried starch as corresponds to 20 gm. of anhydrous starch.

Triturate a quantity of the undried starch, corresponding to 20 gm. of anhydrous starch, with 100 c.c. of water and pour the mixture with stirring into 800 c.c. of boiling water. Boil the mixture for 10 minutes and add sufficient water to make the mixture weigh 1,000 gm., so that it contains exactly 2 per cent. of anhydrous starch.

Dissolve 2 gm. of iodin and 4 gm. of potassium iodid in 250 c.c. of water. Dilute 2 c.c. of this solution to 1,000 c.c. with water.

Dissolve about 2.5 gm. of amylzyme, accurately weighed, in 500 c.c. of water.

In the digestive assays 100 gm. of the starch solution, representing 2 gm. of anhydrous starch, are used for each test. The starch solutions are placed in the thermostat at 40 C., and as soon as their temperature has become stationary small, definite volumes of the dilutions of the enzyme at a temperature of 40 C. are added to the flasks containing the starch paste with the least possible loss of time. The mixtures are well shaken. The volumes of enzyme solution added may be as follows, but each is diluted to that of the largest volume before mixing: 3 c.c., 4 c.c., 5 c.c., 6 c.c and 8 c.c In about eight minutes tests are begun by removing 5 drops from each digesting mixture by a pipet and adding these to 5 c.c. of the dilute iodin solution in a clear, white test tube standing over white paper. It is best to have a row of these tubes mounted to receive the liquids to be tested. At the end of ten minutes if 5 drops from one of the flasks fail to give the iodin reaction a second and more accurate series of tests is carried out. Weigh 100 grams of the paste into each of six flasks, and, assuming that the endpoint in the first test was found at between 3 and 5 c.c., add to the six flasks the following volumes of the diastase solution: 3.4 c.c., 3.6 c.c., 3.8 c.c., 4.0 c.c., 4.4 c.c., and 4.8 c.c. accurately measured. These solutions should all stand ready at a temperature of 40 C. each and diluted with water to 8 c.c., so that they may be poured into the starch and shaken without delay. The tests with the iodin solution are repeated as in the first trial, and new limits are found between which the exact value must lie. For

1. J. Am. Chem. Soc. **30**: 798, 1908.

example, at the expiration of ten minutes the paste to which 3.4 c.c. of the diastase solution had been added may show a faint yellowish, dextrin color, while that with 3.6 c.c. is colorless. A series of new dilutions may be carried out if desired, but practically it is not necessary. In fact, the readings cannot be carried to a much finer degree of accuracy in many cases, because of the difficulty of distinguishing differences between dilutions so near together in color. In a case like the above illustration, it is sufficient to take the mean of the last named dilutions, and calculate the results to the basis of one part of ferment and the number of parts of anhydrous starch converted by it.

The moisture in the starch to be used was first determined. A weight of 1.0038 gm. lost 0.0340 gm., equivalent to 3.47 per cent. A duplicate of 1.0085 gm. lost 0.0335 gm., equivalent to 3.32 per cent. In a third determination 1.2895 gm. of material lost 0.0443 gm., or 3.43 per cent. Average 3.37 per cent. loss. Moisture was also determined in another lot of starch, prepared as described above. A weight of 1.1316 gm. lost 0.0660 gm., equivalent to 5.83 per cent. A duplicate of 1.0637 gm. lost 0.0603 gm., equivalent to 5.67 per cent. Average 5.75 per cent. loss.

A specimen of amylzyme powder and a specimen of the powder as marketed in capusules were examined. The mean of several tests indicated that the powder would convert about 111 parts of starch to the colorless end point in 10 minutes and that the powder in the capsules digested about 80 parts of starch to the same stage in 10 minutes. Another specimen of the powder in capsules which was obtained from the manufacturer was stored for six months before assay. It then converted 108 times its weight of starch. A specimen purchased on the open market and assayed at once converted 121 parts of its weight of dry starch to the colorless end point in 10 minutes.

HOLADIN

Holadin is sold by Fairchild Brothers and Foster. It is stated to be an extractive of the entire pancreas and to exhibit great potency in respect to the several known enzymes, trypsin, amylopsin, lipase and the milk curdling ferment. It is claimed to convert 135 parts of air dry starch to the colorless end point in 10 minutes, if tested by the method described in N. N. R., 1921. This method is essentially the same as the method described by Johnson(see preceding article). except that the values are calculated on undried starch instead of anhydrous starch as the Johnson method prescribes.

A specimen of Holadin was tested by the method as described under the article, Amylzyme, above. The results indicated that Holadin digested only about 82.5 parts of anhydrous starch. As starch does not ordinarily contain more than about 15 per cent. of moisture, the findings, if calculated to a starch containing that amount of moisture, would still be less than claimed.

D-GLUCOSE

During the past few years *d*-glucose has been used considerably in medicine. The parenteral administration of *d*-glucose has been proposed as a means of producing diuresis where other methods have failed and for the determination of sugar tolerance. It has been given with acacia as a means of combating shock. It is readily absorbed as a food whether given by mouth, parenteral or rectal administration.

New and Nonofficial Remedies has described *d*-glucose (under the title of dextrose) for some years, but commercial brands of the article were not listed. Recently specimens of *d*-glucose have been submitted to the Council on Pharmacy and Chemistry for inclusion in New and Nonofficial Remedies. The brands examined were "Anhydrous Dextrose," Digestive Ferments Co. and "*d*-Glucose Pfanstiehl," Special Chemicals Co. The findings are tabulated herewith:

TABLE 1.—EXAMINATION OF D-GLUCOSE
(Pfanstiehl Brand)

	Claimed	Found	Theory
Loss on drying	0.1 per cent.	6.06 per cent.	0
Ash	Negligible	Negligible	0
Optical rotation	+52.5	+51.96	+52.5°

TABLE 2.—EXAMINATION OF D-GLUCOSE
(Difco Brand)

	Claimed	Found	Theory
Loss on drying	0.1 per cent.	0.04 per cent.	0
Ash	0.075 per cent.	Negligible	0
Optical rotation	+52.76°	+52.01°	+52.5°

Based partly upon information furnished by the manufacturer, partly upon that obtained in the examination, and partly upon that in the literature, the following tentative description and standards for *d*-glucose (anhydrous dextrose) were prepared:

ANHYDROUS DEXTROSE. — Saccharum Amylaceum Siccum.—*d*-Glucose Anhydrous.—$C_6H_{12}O_6$. A carbohydrate prepared by the action of dilute acids on starch and subsequent purification. It should contain not less than 98 per cent. of anhydrous dextrose.

d-Glucose is a white, finely granular, odorless powder; taste, sweet; permanent in air. It is freely soluble in water; slightly soluble in alcohol; insoluble in ether or chloroform.

An aqueous solution of *d*-glucose (1: 20) should be clear, colorless, and free from suspended matter. It should be neutral to litmus and should be dextrorotatory. Dilute aqueous solutions of *d*-glucose are readily fermentable and reduce alkaline cupric tartrate solution.

Dissolve about 1 gm. of *d*-glucose in 10 c.c. of water and saturate the solution with hydrogen sulphid. No coloration or precipitation occurs (*absence of the salts of heavy metals*).

Dry about 5 gm. of *d*-glucose to constant weight at 100 C. Dissolve the residue, accurately weighed, in 100 c.c. of water at 20 C. After the solution has stood over night, observe its optical rotation at 20 C., using sodium light. The specific rotatory power should not be less than +51.70°.

Heat about 1 gm. of *d*-glucose, accurately weighed, at 100 C. until it ceases to lose weight. The loss should not exceed 1 per cent.

Incinerate about 1 gm. of *d*-glucose, accurately weighed. Not more than 0.1 per cent. of residue remains.

THEOBROMIN SODIUM ACETATE

Theobromin is an alkaloid occurring chiefly in the seeds of *Theobroma cacao*, the chocolate tree of South America. It has been found in small amounts in the seeds, flowers and leaves of Kola, *Cola acuminata,* and in the leaves of tea, *Thea sinensis.* According to some writers, the seeds of *Paullinia sorbilis*, from which guarana is prepared, also contain it but this is probably not correct. Theobromin occurs in plants in association with caffein. In cacao the theobromin predominates but in the other plants containing theobromin, caffein occurs in the larger proportions. Theobromin may be made synthetically and it is said that the greater part of the alkaloid used is so prepared. It is isomeric with theophyllin. Theobromin is one of the most valued diuretics. It has greater diuretic power than caffein but less than theophyllin. It has the added advantage over caffein that it has little or no action on the central nervous system.

Theobromin is but scantily soluble in the usual laboratory solvents so that its isolation and determination as well as its administration in medicine are matters of difficulty. It combines with alkalies to form soluble compounds such as theobromin sodium, theobromin barium, etc., and this property is utilized in the preparation of theobromin for medicinal uses. Because of its slight solubility, for medicinal use it is usually combined with an alkali and a salt of an alkali thus producing such compounds as theobromin-sodium sodium salicylate, theobromin-sodium sodium acetate, theobromin-sodium sodium formate, etc. For the sake of brevity and euphony, the names of such products are frequently written by omitting the name of the alkali in combination with the alkaloid, e. g., theobromin sodium acetate instead of the

longer term, theobromin-sodium sodium acetate. During past years a number of these combinations have been on the market under fanciful trade names, such as agurin (sodium-theobromin sodium acetate), aniso-theobromin (sodium-theobromin sodium anisate), diuretin (sodium-theobromin sodium salicylate), barutin (barium-theobromin sodium salicylate), eustenin, (theobromin-sodium sodium iodid), theolactin (sodium-theobromin sodium lactate), thephorin (sodium-theobromin sodium formate), urocitral (sodium-theobromin sodium citrate), urogenin (lithium-theobromin lithium hippurate), uropherin (lithium-theobromin lithium benzoate), etc.

Theobromin sodium acetate has been described in New and Nonofficial Remedies for a number of years. In connection with the proposed reacceptance of the article for New and Nonofficial Remedies, 1922, information was furnished by the Powers-Weightman-Rosengarten Company that the market product was not anhydrous as the formula in New and Nonofficial Remedies would appear to indicate. According to the literature, theobromin sodium acetate is a combination of one molecular equivalent of theobromin-sodium with a molecular equivalent of sodium acetate without water of hydration. Since the information from the manufacturer disagreed with that in the literature, it was deemed worth while to make an examination of the market supply of theobromin sodium acetate. Accordingly, a specimen of each of the following brands was examined.

Powers-Weightman-Rosengarten Company (recent specimen).
Mallinckrodt Chemical Works (recent specimen).
Hoffmann-La Roche Chemical Works (received 1915).
Bayer and Company Agurin (received in 1908).
Winthrop Chemical Company. (Agurin Tablets.) (Recent specimen.)

Each specimen (except the tablets) was a white, finely granular, odorless powder; somewhat hygroscopic. The M. C. W. specimen had a distinct yellowish tinge. Each specimen dissolved in warm water, leaving only insignificant amounts of dirt and insoluble matter, with the exception of the M. C. W. specimen which contained appreciable quantities of dirt. This specimen dissolved less readily than othe others. The aqueous solutions of the several specimens each gave a strong alkaline reaction to phenolphthalein and to litmus paper. Each solution gave a white precipitate on the addition f acids. The M. C. W. specimen effervesced strongly with

evolution of carbon dioxid on the addition of acids. No determination of the carbon dioxid in this specimen was carried out but, judging from the rate and amount of the effervescence, the quantity present must have been considerable.

Water of hydration was determined by drying a weighed portion of the material at 100 C. until it ceased to lose weight. Theobromin was determined by direct titration with tenth-normal silver nitrate in a hot, aqueous solution, using potassium chromate as indicator.[1]

Theobromin was also determined by the Emery method.[2] This is as follows:

> Dissolve about 0.2 gm. of the sample, accurately weighed, in a small beaker in 2 c.c. of glacial acetic acid by means of a gentle heat (more acetic acid may be necessary). Dilute the acetic acid solution with 3 to 5 c.c. of hot water. Transfer the perfectly *clear* solution to a 100 c.c. graduated, glass-stoppered flask containing 50 c.c. of tenth-normal iodin, using warm water for rinsing. Next add 20 c.c. of saturated sodium chlorid solution and finally, while rotating the flask, add 2 c.c. of concentrated hydrochloric acid. Stopper the flask and allow it to stand at room temperature over night. Make up to the mark with water and mix thoroughly. Pass the liquid through a small (5.5 centimeter) filter (previously fitted to a funnel by wetting and drying), reject the first 15 c.c. of the filtrate and collect 50 c.c. in a graduated flask. Transfer this aliquot part by pouring and rinsing, to an Erlenmeyer flask of about 250 c.c. capacity, and titrate the excess of iodin with tenth-normal sodium thiosulphate using starch paste as indicator.

One c.c. of N-10 I = 0.0045025 gm. of theobromin.

Sodium was determined by heating a weighed portion of the material with an excess of sulphuric acid, treating the dry residue with a little ammonium carbonate, again heating and finally weighing as sodium sulphate.

The results obtained for the several specimens are tabulated herewith. For comparison the theoretical composition of the salt with and without water of hydration is given in a separate table. In some cases there was a marked difference between the findings for theobromin as determined by the two methods. Owing to lack of time the subject was not pursued further.

Based partially upon the information in the literature and partially upon the results obtained in the examination of the

1. Vulpius: J. Chem. Soc. **58**: 1475, 1890.
2. Emery: J. Eng. Ind. Chem. **10**: 605 (1918).

market products, the following tentative description of theobromin sodium acetate was prepared for New and Nonofficial Remedies:

TABLE 1.—ANALYSIS OF THEOBROMIN SODIUM ACETATE

Brand	Loss on Drying	Theobromin (Yield)	Theobromin (Emery)	Sodium
P. W. R.	13.04	51.77	44.60	15.95
Agurin (old specimen)	16.54	54.64	49.92	14.92
Roche (old specimen)	19.88	49.34	44.43	11.96
M. C. W.	23.72	36.88	36.36	13.25
Agurin tablets	.....	34.89	.....	9.92

THEOBROMIN SODIUM ACETATE.—Theobrominae Sodio-Acetas.—A hydrated, double salt of theobromin-sodium and sodium acetate, containing not less than 50 per cent. of theobromin, corresponding to about 80 per cent. of the anhydrous double salt.—$NaC_7H_7O_2N_4+NaC_2H_3O_2$.

Theobromin sodium acetate is a white, finely crystalline powder; odorless; taste, bitter. It is soluble in cold water; slightly soluble in cold alcohol; more so in hot alcohol. Its aqueous solutions are strongly alkaline towards phenolphthalein and litmus. It is quite

TABLE 2.—THEORETICAL COMPOSITION OF THEOBROMIN SODIUM ACETATE

Formula	Water of Hydration	Theobromin (Yield)	Sodium
$NaC_7H_7O_2N_4 + NaC_2H_3O_2$	0	63.39	16.19
$NaC_7H_7O_2N_4 + NaC_2H_3O_2 + H_2O$	6.6	59.61	15.23
$NaC_7H_7O_2N_4 + NaC_2H_3O_2 + 2\ H_2O$	11.25	56.26	14.37
$NaC_7H_7O_2N_4 + NaC_2H_3O_2 + 3\ H_2O$	15.99	53.25	13.60
$NaC_7H_7O_2N_4 + NaC_2H_3O_2 + 4\ H_2O$	20.23	50.56	12.91
$NaC_7H_7O_2N_4 + NaC_2H_3O_2 + 5\ H_2O$	24.08	48.13	12.29

hygroscopic, and in aqueous solution when exposed to air it gradually splits up into its components. Its aqueous solution is precipitated and decomposed by carbon dioxid and by acids. It forms a bluish-white precipitate with silver nitrate solution, a blue precipitate with copper sulphate solution, and a white one with tartar emetic solution. It is not readily precipitated by mercuric potassium iodid solution or by iodin solution. It is incompatible with carbonated beverages, acids, saccharine and mucilaginous liquids, and most of the alkaloidal reagents.

To 10 cc. of an aqueous solution of theobromin sodium acetate (1: 50) add 2 cc. of dilute nitric acid, filter and add a few drops of silver nitrate solution to the filtrate. Not more than an opalescence results (*limit of chlorid*).

Dry about 1 gm. of theobromin sodium acetate, accurately weighed, to constant weight at 100 C. The loss does not exceed 20 per cent.

Dissolve about 1 gm. of theobromin sodium acetate, accurately weighed; in 100 cc. of warm water, add phenolphthalein solution and titrate with normal hydrochloric acid to the disappearance of the pink color. Not more than 3 cc. of normal acid should be required for each gm. of substance taken (*limit of alkali*).

Dissolve about 0.25 gm. of theobromin sodium acetate, accurately weighed, in 100 cc. of hot water, add a few drops of potassium chromate solution and titrate the solution while hot with tenth-normal silver nitrate to the formation of a reddish color. The tenth-normal silver nitrate consumed corresponds to at least 50 per cent. of theobromin.

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The names of authors appear in capitals, under which will be found the titles of their signed articles. Under the names of the proprietors appear the respective products to which reference is made. The names of the products also occur in alphabetical sequence.

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